Advanced Wound Care Adhesives with New Functional Properties

Chiaula, Valeria

Publication date: 2020

Document Version
Publisher's PDF, also known as Version of record

Link back to DTU Orbit

Citation (APA):
Ph.D. Thesis

Advanced Wound Care Adhesives with New Functional Properties

Valeria Chiaula

July 2020

DTU Chemical Engineering
Department of Chemical and Biochemical Engineering
Technical University of Denmark
Søltofts Plads 229
2800 Kongens Lyngby, Denmark
Phone +45 4525 2800

www.kt.dtu.dk
Preface

This thesis entitled “Advanced Wound Care Adhesives with New Functional Properties” has been written to partially fulfil the requirements for obtaining the Ph.D. degree at the Technical University of Denmark. The thesis summarizes the scientific work that I, Valeria Chiaula, have carried out during the Ph.D. project. In order to fulfil all the requirements to obtain a Ph.D. degree at the Technical University of Denmark, I have also taken courses worth 28 ECTS points, been a supervisor of undergraduate students, participated in and presented (both orally and with posters) at various international conferences, and last but not least, publicly defended my thesis.

The work presented in this Ph.D. thesis has been conducted both at Coloplast A/S and at DTU – Chemical Engineering in the research centre The Danish Polymer Centre. The work have been carried out from August 2017 to August 2020 under the supervision of Professor Anne Ladegaard Skov and company co-supervisor Principal Scientist Anders Christian Nielsen. The project was funded by Coloplast A/S and Innovationsfonden.

Valeria Chiaula
Kongens Lyngby
July 31, 2020
Valeria Chiaula
Acknowledgements

First and foremost, I would like to thank my supervisor Professor Anne Ladegaard Skov for all your help and guidance throughout the entire PhD project. I wish to express my sincere gratitude for your invaluable guidance, which have allowed me to stay on the right track during the project. Your door and your Teams channel were always open for a discussion, whenever I wanted to discuss science and/or personal things. Your extensive knowledge and skills as a supervisor taught me many great things, which I will certainly carry with me in my future carrier.

Next, I would like to thank my co-supervisor Principal Scientist Anders Christian Nielsen for introducing me to the workplace at Coloplast and always making me feel welcome here. Not only you contributed with your great knowledge on silicones within the industrial field, but also you have always ensured that nothing was missing to carry out my project in the best possible way. I was never missing chemicals and materials, and you have always helped with contacting people to fulfil my various tasks.

Additionally, I would also like to thank my co-supervisor Researcher Piotr Stanislaw Mazurek for the help you gave in the laboratory through your knowledge and skills. You have taught me to believe in myself and become a confident, independent scientist.

I would like to say a big thanks to my Coloplast colleagues, Ludovica, Anca, Karolina, Aga, Sim, Bahar, Sofie, Daniel H., Daniel B., Johannes, Jakob, Jose and Irakli. You always made me feel a great part of our amazing team at Coloplast. Thanks for all the special moments inside and outside Coloplast. A big extra thanks to Daniel H. and Johannes, who shared with me the journey to be an industrial PhD. I appreciated so much all the scientific discussions we had and the knowledge we gained from each other. Special thanks go to Lotte Stoklund Jensen, Esben Strøbech, Rasmus Irming Jølck and Henrik Edvardsen. Not only you helped me to carry out a successful PhD throughout your great assistance in the lab, but also you contributed to my growth as a scientist throughout the great exchange of ideas and science we had during my PhD.

To my amazing DPC family, especially to Justina, Alena, Sara, Elisa, Rene, Libor, Jakob, Jeong, Christian, Bjørn and Jeppe. You have been always my reason to smile and be happy here in Denmark. I could have never wished to meet better friends than you. With you, I never felt like if I was missing home, because you became my home. I am so thankful for all the happy moments we had both at DPC and outside. I wish we will stick together for the rest of our lives. Special thanks to Jeppe, for everything.

To my best friends in Italy, Federica, Giorgia, Emanuela, Francesca, Matteo, Lorenzo, Andrea, Alessia, Stefania, Giulia, Ilaria, Angela, Alessandra, Graziella, Davide, Andrea, Camilla, big thanks because you have always filled these 2000 km that separate us. You were and are always with me. You made me stronger in these years, always reminding me where I came from and making me proud of that. You taught me that we are never far away from each other, if our hearts are close.

To my new Italian friends in Denmark, Valerio, Diana, Lorenzo, Beatrice, Irene, Daniele, Umberto, Oriana, Fabio, Lidia, Piero and Edoardo. Thanks because you have been a fundamental
part of this journey. You have been always there for me. Thanks for all the Sundays together, for all the laughs and the joy that you fill my heart with. My life in Denmark would not be the same without my new Italian family.

I would like to thank my family, my mum Silvia, my dad Vincenzo, my brother Marco and my aunt Monica, for always believing in me, encouraging me, and supporting me, and for daring to ask me what I was working with, always with a big smile. Thanks because you allowed me to have blown my life, you have never stopped my dreams and you have always told me: “Be who you are, do whatever you want, the important is that you are happy”. You are my home, and home is where my heart is, always with you.

Finally, to the love of my life and my partner, Alfredo. You found me at the half way of this journey and you never let me go. Thanks for being there every single day, for listening to me, for being with me in my best days, but especially in my worst days. Thank you for always holding my hand in this big part of my life, for helping me and for making me see things from different perspectives. If today I have reached this achievement, it is also because of you. Thank you, because you also supported me preparing always my favorite dishes. And thank you, for sharing with me new adventures around the world. You are my light, my safe heaven and my new solid foundation of my life.

Valeria Chiaula
Kongens Lyngby
July 31, 2020
Abstract
An increasing number of patients, globally, suffers from chronic wounds as a consequence of diabetes or other chronic diseases that may interfere with a correct wound healing. When not effectively treated, chronic wounds can lead to significant disability, limb amputation, and increased mortality. In addition, the outbreak of severe bacterial infections is one of the major complications related with chronic wounds. Such conditions affect patients’ life not only physically, but also socially, since patients often experience depression, fear, and social isolation. Moreover, chronic wounds management economically affects the medical system due to the high costs of medical treatments. Therefore, advanced wound care solutions, which effectively promote wound healing while preventing bacterial infections, are sought after.

Pressure sensitive adhesives (PSAs) are a broad class of materials used in several applications. For wound care applications, PSAs are required to be soft, viscoelastic solids. Among PSA materials, silicone adhesives are particularly sought after amongst wound care industry. Silicone adhesives possess gentle skin adhesion properties along with other unique properties of silicones, such as flexibility, chemical inertness and biocompatibility. In addition, silicone adhesives are considered atraumatic since their removal from the skin is easy and residue-free. In general, skin adhesives should allow for moisture transmission at the skin-adhesive interface to avoid skin maceration. Due to large mobility of the polymer chains, silicone adhesives possess high oxygen permeability and water vapor transmission rate (WVTR). However, due to their inherent hydrophobicity, current silicone adhesives for wound care are challenged when it comes to fluid handling. In addition, as silicones attach poorly to moist surfaces, basic perspiration from the user’s skin can cause the silicone to lose its adhesive properties, resulting in undesired failure of the skin adhesive.

Therefore, in the first part of the project, the main goal is to improve both permeability and water absorption of silicone adhesives. This is achieved by the incorporation of emulsified glycerol into silicone adhesives, developing a novel, industrially relevant glycerol-silicone hybrid adhesive. The glycerol-silicone adhesives are created simply by providing high shear forces to mixtures of glycerol and silicone adhesive premix. This allows the formation of physically stable glycerol-in-silicone emulsions, which upon cross-linking of the silicone phase, form free-standing two-phase adhesives. It is demonstrated that the incorporation of glycerol into silicone adhesives significantly improves both the permeability and the water absorption, without compromising the mechanical properties of adhesives and also peel and tack. This is mainly due to the so-called solid stiffening effect given by the glycerol droplets as a result of their interfacial energies. In addition, the adhesive performance during realistic perspiration conditions is investigated.

In the final phase of this project, the incorporation of the antiseptic drug octenidine via cyclodextrins into glycerol-silicone adhesive, its release and antimicrobial properties are investigated. The chemical structure of octenidine presents long alkyl chains and two amine groups. As the crosslinking of glycerol-silicone adhesives occurs via hydrosilylation reaction, the amine groups constitute a threat for the sensitive platinum (Pt) catalyst and thus inhibits the reaction. It is shown that cyclodextrins suppress the interference of octenidine with the Pt Catalyst,
likely through the formation of an inclusion complex between octenidine and cyclodextrins. A patent was recently filed on this new technology.

**Resumé**


# Table of Contents

Preface ........................................................................... iii
Acknowledgements ................................................................. iv
Abstract ........................................................................... vi
Resumé ........................................................................... vii
Table of Contents ................................................................... viii

1. Introduction to the Thesis ......................................................... 1
   1.1 Publications ...................................................................... 1
   1.2 Patents ........................................................................... 1
   1.3 Conference Contributions ...................................................... 1
   1.4 Project Supervision ............................................................ 2
   1.5 Thesis Outline and Objectives ............................................. 2

2. Chronic Wounds ................................................................ 4
   2.1 Wound Healing and Pathogenesis of Chronic Wounds .......... 5
   2.2 Chronic Wounds and Bacterial Infections ................................. 5
   2.3 Industrial Relevance of the Project ........................................ 7

3. Principles of Adhesion and Adhesives ................................. 9
   3.1 Principles of Adhesion ....................................................... 9
   3.2 Thermodynamic Theory, Wetting Criteria and Work of Adhesion ........................................ 10
   3.3 Adhesives in Wound Healing: Pressure Sensitive Adhesives ........................................ 11
   3.4 Adhesion of viscoelastic materials ............................................. 12
   3.5 Peel and Tack .................................................................. 12
   3.6 Silicone Adhesives ............................................................. 14
   3.7 Why Silicone Adhesives in Medical Applications? ....................... 15
   3.8 Hydrosilylation Cured Silicone Adhesives ............................... 15
   3.9 Cyclodextrins .................................................................. 17

4. Glycerol-Silicone Adhesives with Improved Fluid Handling Properties ........................................ 19
   4.1 Introduction ..................................................................... 19
   4.2 Experimental .................................................................... 20
      4.2.1 Materials ..................................................................... 20
   4.3 Methods .......................................................................... 21
      4.3.1 Sample Preparation ......................................................... 21
4.3.2 Morphology of Glycerol-Silicone Adhesives and Determination of Glycerol Surface Area per Volume of Adhesive ................................................................. 21
4.3.3 Fluid Handling Capability of Adhesives ................................................................. 22
4.3.4 Linear Viscoelastic Measurements ....................................................................... 22
4.3.5 Peel Tests on Stainless Steel Plates and Pig Skin ................................................. 22
4.3.6 Perspiration Simulator and Perspiration Experiments ......................................... 23
4.3.7 Tack Tests ........................................................................................................... 23
4.4 Results and Discussion ......................................................................................... 24
4.4.1 Morphology of Glycerol-silicone Adhesives and Determination of Glycerol Surface Area per Volume of Adhesive ................................................................. 24
4.4.2 Water Absorption and Permeability ................................................................. 26
4.4.3 Linear Viscoelastic Properties of Glycerol-Silicone Adhesives ............................... 28
4.4.4 Peel Force Analysis of Glycerol-Silicone Hybrid Adhesives on Stainless Steel Plates ................................................................. 29
4.4.5 Peel Force Analysis of Glycerol-Silicone Adhesives on Pig Skin ............................. 30
4.4.6 Perspiration Experiments and Adhesives’ Performance Characterization ............ 32
4.4.7 Tack Force Analysis of Glycerol-Silicone Hybrid Adhesives ................................. 33
4.5 Conclusions ........................................................................................................... 34
5. Novel Antimicrobial Glycerol-Silicone Adhesives ..................................................... 35
5.1 Introduction ........................................................................................................... 35
5.2 Experimental ......................................................................................................... 37
5.2.1 Materials .......................................................................................................... 37
5.3 Methods ............................................................................................................... 38
5.3.1 Sample Preparation ............................................................................................ 38
5.3.2 Curing Profiles of Glycerol-Silicone Adhesives and Linear Viscoelastic Measurements ................................................................. 39
5.3.3 Morphology of Glycerol-Silicone Adhesives ....................................................... 39
5.3.4 NMR Studies ................................................................................................... 39
5.3.5 Release Profiles of Glycerol-Silicone Adhesives ................................................ 39
5.3.6 Antimicrobial Properties of Adhesives ............................................................. 40
5.4 Results and Discussion ......................................................................................... 40
5.4.1 Investigation of The Best Molar Ratio CDs:Oct through The Evaluation of The Curing Profiles of Glycerol-Silicone Adhesives ................................................................. 40
5.4.2 2D ROESY of HPβCD:Oct Complexes ................................................................ 42
5.4.3 Evaluation of The Linear Viscoelastic Properties of Glycerol-Silicone Adhesives Containing CDs:Oct Mixtures ................................................................. 44
5.4.4 Release profiles of Oct from glycerol-silicone adhesives and antimicrobial activity ................................................................. 49
Preface

5.5 Conclusions

6. Conclusion and Outlook
   6.1 Conclusions
   6.2 Outlook

Abbreviations

Bibliography

Appendix A

Appendix B
1. Introduction to the Thesis

In this chapter the publications, patents and conference contributions within the present PhD project are listed. Furthermore, a list of the supervised student projects is given, along with an outline of the present thesis.

1.1 Publications

Peer-Reviewed Journals:


1.2 Patents


Filing date: 6th of July 2018.

Title: Elastomeric silicone compositions comprising glycerol, cyclodextrin and octenidine.

Applicant: Coloplast A/S.


1.3 Conference Contributions

Oral presentations:


- V. Chiaula, P. Mazurek, J. Eiler, A. C. Nielsen, A. L. Skov “Hybrid glycerol-silicone adhesives with excellent moisture handling properties for advanced wound care

Poster presentations:


### 1.4 Project Supervision

Internship project of:


### 1.5 Thesis Outline and Objectives

When dealing with chronic wounds, silicone adhesives are currently the preferred skin adhesive system due to their gentle skin adhesion properties. Due to the mobility of the polymer chains and low surface tension, silicones adapt and conform to the uneven skin in a comfortable fashion. In addition, silicone adhesives possess excellent oxygen and water vapor permeability. However, due to its inherent hydrophobicity, silicone is challenged when it comes to absorb excessive amounts of liquid from the skin/wounds (e.g. sweats, wound exudates). If the amounts of liquids overcome the fluid handling capability of the adhesive, the latter will lose adhesive properties and eventually fall off.

The main objective of this PhD thesis was therefore to develop a new, industrially relevant silicone adhesive with improved fluid handling properties. This was to be achieved through the incorporation of emulsified glycerol into the silicone adhesive matrix. Contrarily to the hydrophobic silicone, glycerol droplets caused the water to be absorbed in significant amounts. Overall, the new glycerol-silicone hybrid adhesive significantly improved both water absorption and permeability compared to a pristine silicone adhesive.

The second objective of this project was to use the new glycerol-silicone adhesive as system for releasing active compounds with antimicrobial properties. The chosen compound was the cationic antiseptic octenidine, which possesses two amino groups in its chemical structures. As the amino groups are inhibitors of the platinum catalyst involved in the hydrosilylation reaction used to cure
silicone adhesives, the incorporation of octenidine was challenging. Therefore, a new method to cure glycerol-silicone adhesive through hydrosilylation in the presence of the platinum-inhibiting octenidine was developed.

**Chapter 2** gives a general introduction on chronic wounds and wound healing. The relevant aspects of the chronic wounds management, as well as the pathogenesis of chronic wounds, are described. In addition, the complications related with bacterial infections occurring in chronic wounds are discussed in this chapter.

**Chapter 3** describes initially describes the principles of adhesion, with focus on the thermodynamic theory of adhesion. Even though other theories describing the adhesion mechanism exist, I chose to focus on the thermodynamic one, since I believe it is the most relevant to understand the adhesion forces and the interesting properties of the glycerol-silicone adhesives. Secondly, the chapter continues with an introduction on pressure sensitive adhesives, with focus on silicone adhesives used in wound care applications.

**Chapter 4** is the published peer-reviewed article with the title “Advanced wound care adhesive with new functional properties”. Herein, the development of the new glycerol-silicone hybrid adhesives with improved fluid handling properties is described. It is described how the emulsified glycerol incorporated into silicone significantly improved both water absorption and permeability of adhesives. In addition, it also shown that the relevant adhesive properties, such as peel and tack, were not compromised by the presence of glycerol in the silicone. The adhesive performance under perspiration simulations experiments is also described.

**Chapter 5** is the final manuscript submitted to the Journal “ACS Applied Polymer Materials”, which refers also to the patent application filed in May 2020 with the title “Elastomeric silicone compositions comprising glycerol, cyclodextrin and octenidine.” Herein, the development of a new strategy to cure glycerol-silicone adhesives through hydrosilylation in the presence of octenidine is described. Successful curing in the presence of this platinum-inhibiting molecule was achieved through the formation of inclusion complexes with cyclodextrins. Through rheological investigation, it was demonstrated that cyclodextrins suppress the interference of octenidine with the platinum catalyst involved in the hydrosilylation. Finally yet important, the release of octenidine from the adhesive, and consequently its antimicrobial properties, are described.

**Chapter 6** is the overall conclusion of this PhD thesis. Suggestions on how to further improve and investigate glycerol-silicone adhesives are presented.

**Appendix A** contains the published article in the journal layout and the supplementary information relevant for Chapter 4.

**Appendix B** is the copy of the submitted manuscript of Chapter 5 with supplementary information.
2. Chronic Wounds

Chronic wounds are generally defined as wounds that have not healed for six weeks or more and include pressure ulcers (PU), venous leg ulcers (VLU), and diabetic foot ulcers (DFU) \(^1\)–\(^4\). Examples of chronic wounds are illustrated in Table 1. Partly due to continuously growing population of elderly citizens, chronic wounds are often manifested in elderly patients. However, these wounds are also associated with complications of illnesses as diabetes mellitus \(^5\). When not treated effectively, chronic wounds severely affect patients’ life as they cause pain, decreased mobility, leak fluid, limb amputation, dangerous infections, and increased mortality. Having a PU increases mortality by 7.23 % mainly due to infections \(^3\), and patients with a DFU have a higher 5-year mortality risk (45% - 55 %) than patients with breast cancer (18 %) \(^6\). As a consequence, also the social life of patients is affected, since those symptoms can lead to anger, fear, social isolation, and depression. Furthermore, chronic wound are a serious burden not only for the patients, but also for the medical system. In the US alone, over 6 million people are affected by chronic wounds every year, costing up to $25 billion in treatment costs \(^2\). For all these reasons, developing wound care products that effectively promote healing of chronic wounds would be beneficial to reduce costs associated with the treatments, but more importantly to improve the quality of life of affected patients. To do so, a deeper understanding of the wound healing mechanism and the complications related to chronic wounds is needed.

<table>
<thead>
<tr>
<th>Type of Wound</th>
<th>Appearance</th>
<th>Clinical Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic Foot Ulcer</td>
<td>![Image]</td>
<td>Anywhere on the feet</td>
</tr>
<tr>
<td>Venous Leg Ulcer</td>
<td>![Image]</td>
<td>Medial malleolus</td>
</tr>
<tr>
<td>Pressure Ulcer</td>
<td>![Image]</td>
<td>Over bony prominences (e.g. sacrum)</td>
</tr>
</tbody>
</table>
2.1 Wound Healing and Pathogenesis of Chronic Wounds

Wound healing is a dynamic and complicated process characterized by three sequential yet overlapping cellular phases: hemostasis/inflammation, proliferation, and remodeling \cite{7,8}. When skin is injured, the first phase occurs. The exposed injured sub-endothelium activates platelet aggregation in order to form the clot and achieve hemostasis. At the same time, the first cells in charge of removing damaged tissue and bacteria reach the injury site, providing a good environment for wound healing. The hemostasis/inflammation phase lasts approximately 72 h \cite{9,10}. The following proliferative phase provides many cells, including fibroblasts, keratinocytes and endothelial cells, designated to build granulation tissue. This granulation tissue is built upon the so-called extracellular matrix (ECM), which replaces the clot formed during the first phase \cite{8,11}. The proliferative phase can take up to few weeks. In the last phase, the remodeling phase, gradual degradation of ECM and formation of new collagen occur. This phase can continue for few months, but also years \cite{12}.

Chronic wounds result from anomalies in the cellular and molecular wound healing mechanism. Numerous molecular and biochemical imbalances occur within the chronic wound environment, for instances overexpression of certain cells type or low activities of others \cite{13,14}. These imbalances are mainly found in the first two phases of wound healing. For this reason, chronic wounds are often referred as “stuck” in the inflammatory of proliferative phase \cite{13}. However, any aberration in the remodeling phase may lead to chronic wounds as well \cite{15}.

2.2 Chronic Wounds and Bacterial Infections

The negative effect of bacterial infections on wound healing has been recognized for decades and the management of the bioburden is essential to prevent serious complications in chronic wounds \cite{16,17}. Bacteria have developed efficient ways to protect themselves from the surrounding environment by being able to adhere to both biotic and abiotic surfaces. During the surface attachment process, bacteria build up a protective matrix consisting of various biomolecules, such as proteins, polysaccharides, extracellular DNA and lipids, known as biofilm \cite{18}. The biofilm formation includes 4 steps: 1) attachment; 2) formation of an early biofilm; 3) formation of a mature biofilm; 4) dispersion. An illustration of the steps of biofilm formation is presented in Figure 2.1.
**Figure 2.1.** Illustration of the steps of biofilm formation. 1) Attachment. 2) Formation of an early biofilm. 3) Formation of a mature biofilm. 4) Dispersion.

In the first step, bacteria move closely to the surface by using tail/hair-like appendages called flagella or pili. Subsequently, the adsorption of bacteria on the surface occurs mainly due to van der Waals forces, electrostatic, and steric interactions. In the second step, some of the bacteria become irreversibly attached to the surface, forming an early biofilm. Thirdly, bacteria are able to communicate through a mechanism known as “quorum sensing”; a cascade of signaling molecules is produced, which induce different biological pathways involved in the mature biofilm formation. The formation of the biofilm occurs rather quickly (within hours), and the maturation and growth of the biofilm continues forming bacterial culture nearly up to 100 µm tall. In the last step, the dispersion of biofilm involves bacteria releasing itself from the biofilm matrix, returning to the first step, and finding new surfaces to colonize. Some of the most common bacterial strains found in chronic wounds are *Staphylococcus Aureus*, *Pseudomonas Aeruginosa*, and *Escherichia Coli*.

Research over the past two decades has shown that many persistent infections in chronic wounds result from biofilm formation. Biofilm-related infections are rarely solved by immune defenses and they induce a state of excessive or inappropriate inflammation in the body. Persistent inflammation is one of the causes of delayed healing in chronic wounds. In addition, as biofilms can be formed by multiple colonies of different bacteria, biofilm-related infections can be difficult to treat with traditional antibiotics due to increased antibiotic resistance. In worst cases, these infections
infections can be lethal \(^{16,17,27,28}\). Antibiotic resistance can be given by biofilm matrix production, microbial mutation, and frequent use of antibiotics \(^{26,29}\).

In general, a microbiological analysis of the bacteria strains colonizing the wound site would be beneficial before proceeding with antibiotic treatments of infections in chronic wounds. Either systemic or topical agents can be used for the treatments of infections in chronic wounds. The use of topical antibiotics and antiseptics to fight bacterial infections in chronic wounds can offer several advantages over systemic administration. For instance, it is possible to target the delivery of high concentration of antibiotic directly to the infection site while reducing a potential systemic toxicity \(^{30–32}\).

### 2.3 Industrial Relevance of the Project

Coloplast is one of the world-leading supplier of intimate healthcare products and services. Business mainly includes three areas: Ostomy Care, Urology and Continence Care, and Wound and Skin Care (this is the area related to this Ph.D thesis). Divisions for specific sectors and share of revenue can be seen in **Figure 2.2**.

![Revenue](image)

**Figure 2.2.** Coloplast revenue by segment of full year 2018/19.

Coloplast is one of the global market leaders in the advanced wound care market, having a market share of 5-10 %. As the global wound care market is highly competitive, new technological solutions addressing chronic wounds are constantly sought after. Core products from Wound and Skin care are shown in **Figure 2.3**.
Figure 2.3. Coloplast core products from Wound and Skin Care.
3. Principles of Adhesion and Adhesives

In order to promote efficient wound healing and to avoid serious outbreaks of infections, skin adhesives that create and maintain a correct wound environment play a significant role. Wearing a skin adhesive comes along with some challenges. One of these challenges is to maintain good periwound skin health. Periwound skin damage can be a consequence of frequent change of skin adhesives where each change exfoliates and damage the skin. Furthermore, if the adhesives attach poorly, leakage of wound exudates can cause skin irritation. In contrast, if the adhesion is too strong, the removal of skin adhesives is associated with pain and trauma, leading to mental fear of the user worrying to experience pain.

Consequently, skin adhesives used in chronic wound management must satisfy several requirements. The adhesive must adhere easily to the wound bed, providing sufficient adhesion to ensure long performance. At the same time, its removal must be easy without leaving residues on the skin. The adhesive must adhere gently on the periwound skin to avoid damage of that during removal, but it must also adhere when the user is sweating and therefore sweat is released at the skin-adhesive interface. This means that the ideal adhesive must have sufficient permeability and liquid absorption properties to handle the liquids coming from skin/wound without losing adhesive properties. In other words, the ideal skin adhesive must maintain the right moisture balance at the wound site, absorbing excessive liquids coming from the skin/wound but also providing hydration. Finally, the adhesive should protect the wound from bacterial attachment.

3.1 Principles of Adhesion

Adhesion occurs when two surfaces are held together by interfacial forces. To describe what interfacial forces are, it is important to recall the concepts of wettability, cohesive forces, adhesive forces and surface tension. Wettability is defined as the adhesion of a liquid to a solid. Cohesive forces act between molecules of the same substance. Specifically, if referring to a droplet of liquid, cohesive forces hold the droplet together. On the other hand, adhesion forces act between molecules of different substances. If wetting of a solid substance is required, adhesive forces must prevail on cohesive forces. In other words, if a liquid is put onto a solid surface, adhesion takes place if the liquid molecules tend to spread over the solid surface rather than being attracted to other liquid molecules. Still referring to a droplet of liquid, the concept of surface tension can be now introduced. In the center of a droplet of liquid, molecules are very similar to each other; therefore, the cohesive forces acting between them are equal in all the directions and repeal each other. In contrast, at the surface of the droplet, any external forces do not counterbalance the cohesive forces that pull molecules internally. This condition creates the typical spherical shape of a droplet of liquid and cause the molecules at the surface to have an excess of potential energy. This excess of energy per unit area is the surface tension. Liquids with high surface tension possess strong cohesive forces between liquid molecules. Also solids have a surface tension, or surface-free energy. As solids possess stronger bonds between molecules, surface tension does not cause the same deformation observed in liquids, but it is acting when two solid surfaces are in contact.
The interactions between a liquid and a solid or two solids can be referred as interfacial forces or interfacial tension. The more similar the nature of the surface forces between a liquid and a solid or two solids, the lower the interfacial tension and the higher the chance that a material will spread over the other. This is important to keep in mind when considering skin adhesion of wound care adhesives.

### 3.2 Thermodynamic Theory, Wetting Criteria and Work of Adhesion

The thermodynamic, or adsorption, model of adhesion describes the adhesion between two substrates in intimate contact as result of interatomic and intermolecular forces established at the interface. In order to describe the wetting phenomenon, a droplet of liquid on a planar solid substrate is considered (see Figure 3.1).

![Figure 3.1. Schematic illustration of liquid-solid wetting phenomenon. Wettability is considered in terms of the contact angle (θ) on the liquid on the solid.](image)

The surface tension $\gamma$ of a material at the three-phase contact point is related to the equilibrium contact angle $\theta$ and it is described by Young’s equation as

$$\gamma_{SV} = \gamma_{SL} + \gamma_{LV} \cos(\theta)$$

(1)
Chapter 3 – Principles of Adhesion and Adhesives

The subscripts $S$, $L$ and $V$ stand for solid, liquid and vapor phase, respectively, while a combination of two of them indicates to a given interface – for instance, $SV$ indicates the solid – vapor interface. The term $\gamma_{SV}$ corresponds to the surface tension of the solid after the equilibrium absorption of vapor from the liquid. Sometimes, $\gamma_{SV}$ is lower than $\gamma_S$, which is the surface tension of the solid in vacuum. The difference between $\gamma_S$ and $\gamma_{SV}$ is called spreading pressure of the vapor onto the solid $^{38}$. Often the spreading pressure is negligible for polymer materials, thus it is possible to use $\gamma_S$ instead of $\gamma_{SV}$. If $\theta > 0^\circ$, the liquid does not spread over the solid, whereas spontaneous spreading occurs when $\theta = 0^\circ$. Therefore, the conditions for spontaneous wetting can be written as

$$\gamma_S \geq \gamma_{SL} + \gamma_{LV} \quad (2)$$

or

$$S = \gamma_S - \gamma_{SL} - \gamma_{LV} \geq 0 \quad (3)$$

where $S$ is the spreading coefficient.

The work of adhesion $W_{SL}$, according to Eq. (1) and Dupré’s relationship $^{39}$, is then defined as

$$W_{SL} = \gamma_S + \gamma_{LV} - \gamma_{SL} = \gamma_{LV}(1 + \cos \theta) \quad (4)$$

thus, it is directly related to the contact angle $\theta$.

When considering a system liquid-solid, it is also important to describe the nature of the forces of attraction between the liquid molecules and the solid, thus the nature of the interfacial tension. As mentioned in the previous section, the more alike the forces between the liquid and the solid, the higher the spreading of the liquid over the forces. Schultz et al $^{40}$ proposed that the surface tension $\gamma$ can be described by two components, namely a polar component $\gamma_P$ and a dispersive (non-polar) component $\gamma_D$:

$$\gamma = \gamma_P + \gamma_D \quad (5)$$

Now, it is possible to define all the components that characterize the interfacial tension $\gamma$ between two phases in a system liquid-solid. For simplicity of the terminology, the liquid and the solid are called 1 and 2, respectively. Thus, the interfacial tension $\gamma_{1,2}$ is defined as

$$\gamma_{1,2} = \gamma_1 + \gamma_2 - 2(\gamma_{1D}\gamma_{2D})^{1/2} - 2(\gamma_{1P}\gamma_{2P})^{1/2} \quad (6)$$

where $\gamma_{1D}$ and $\gamma_{2D}$ are the dispersive components of the liquid and the solid, and $\gamma_{1P}$ and $\gamma_{2P}$ are the polar components of the liquid and the solid $^{41-43}$.

### 3.3 Adhesives in Wound Healing: Pressure Sensitive Adhesives

Pressure sensitive adhesives (PSA) are a class of polymeric materials that adhere to almost any type of surface by applying a light pressure $^{44,45}$. Also, the bonding process of a PSA to a surface does not involve any chemical reaction, activation by heat or removal of solvent, therefore indicating that the safety of use of the materials is a requirement. When a molecular contact is
established between a PSA and a substrate, interfacial forces mainly govern the adhesion, typically van der Waals forces. Generally, PSAs used in wound care applications should be soft, viscoelastic solids. Soft, because they must adapt to human skin, which is an uneven surface, in a comfortable fashion, and solid because they must have enough cohesive strength to maintain the bond until removal. The debonding process of PSAs can be described by the thermodynamic work of adhesion, which is the difference between the energy gained in forming the bonding (adhesion) and the energy dissipated during the removal.

In the following sections, the adhesion of viscoelastic materials and some of the relevant properties of adhesives, such as peel and tack, are discussed.

3.4 Adhesion of viscoelastic materials

To remove an adhesive from a substrate, e.g. skin, the required energy is usually greater than the work needed to apply the adhesive to the substrate. This a typical behavior of viscoelastic polymers and it is known as adhesion hysteresis. When the adhesive is removed from the substrate, the energy dissipated during debonding causes the adhesion hysteresis. The dissipation energy results from polymer chain reorganization, which is caused by deformation of the adhesive upon removal. As adhesives possess an intrinsic viscous component, both the dissipation energy and the adhesive properties depend on the rate of removal. To describe the adhesion of viscoelastic materials, Gent and Schultz proposed the following model:

\[ G = W_{ad} \phi (a_T V) \]  

(7)

where \( G \) corresponds to the total adhesion energy, \( W_{ad} \) is the thermodynamic work of adhesion, \( \phi \) is the dissipation energy, \( a_T \) is time-temperature shift factor, and \( V \) is the separation rate. This model establishes that the total adhesion energy is proportional to the thermodynamic work of adhesion and the dissipation energy:

\[ G \propto W_{ad} \phi \]  

(8)

Thus, both the bulk mechanical properties and the surface properties of adhesives define the adhesive performance. Rheology analysis can be a good tool to evaluate both elastic and viscous properties of adhesives and predict the adhesive performance. In 2009, Jensen et al demonstrated that there is a relation between the peel force and the loss tangent of PSAs. A thorough investigation of the dependency of the peel and adhesive performance on the bulk rheological properties was one of the relevant scientific achievements of this PhD thesis and it is described in Chapter 4.

3.5 Peel and Tack

One of the properties most often measured to evaluate both adhesives’ performance and the quality of their adhesive bonds is the resistance to peel in relation to a given substrate. Analysis
of peel forces can be used to describe the quality of the adhesive bond to a given substrate, and is therefore helpful in comparing different adhesive materials. In a standard peel test, often used to quantify long-term adhesive performance, a strip of adhesive is put into contact with the substrate for a set amount of time, usually 30 minutes. The strip is subsequently peeled at constant peel rate and at a specific peel angle, usually 90° or 180°. During peel experiments, it is very important to distinguish between two types of failure modes: namely, adhesive and cohesive failure. Adhesive failure occurs when the adhesive peels off cleanly from the substrate without leaving any visible residue. Cohesive failure occurs when adhesive residue remains on the on the substrate after peeling (see Figure 3.2).

**Figure 3.2.** Schematic illustration of adhesive (left) and cohesive (right) failure modes. Adhesive failure occurs when the adhesive peels off cleanly from the substrate. Cohesive failure occurs when visible adhesive residue remains after removal from the substrate.

While cohesive failure is typically associated with defects in adhesive product, it is important to note that the two types of failure are also temperature- and rate-dependent. Adhesive failure is generally observed at room temperature and/or standard peel rate (5 mm/s), whereas cohesive failure is more likely to occur at high temperature and/or low peel rate, both of which cause a more viscous deformation. Some adhesives can therefore exhibit both types of failure depending on the test conditions. The transition from one failure mode to the other is quite complex. Because the peel test causes a large deformation and stress of the adhesive at the peel front, it is logical to assume that the shape of the peel front is influenced by the adhesive thickness, the bulk rheological properties of the adhesive and the peel rate.

To evaluate short-term adhesive performance, a tack test is commonly employed. Similar to peel, tack is a crucial property of PSAs because it quantifies their inherent ability to form an immediate bond when put in touch with a surface. An adhesive meant for wound care applications, for example, requires a minimum level of tackiness. When dealing with wounded and/or fragile skin, using high pressures to apply the adhesive to the skin can cause further trauma and/or pain. The appropriate level of tackiness will therefore ensure an instant bond to the skin under light pressure. In tack tests, although it is important to achieve an immediate bond to a substrate, it is equally important that the debonding proceeds smoothly — i.e. with no visible residue on the substrate.
after separation. Over the years, several methods have been developed to measure tack, the most common of which are probe tack, quick stick, rolling ball and loop tack tests.

### 3.6 Silicone Adhesives

Among all PSAs, silicone adhesives can be considered a niche product; usually more expensive than other PSAs, they are typically used when high performance materials are required, that is when dealing with chronic wounds and very fragile skin.

Silicones, or polysiloxanes (chemical formula \([R_2SiO]_n\) where \(R = \) organic groups), possess a unique inorganic-organic structure: an inorganic silicone oxygen backbone (-\(\text{Si} – \text{O} – \text{Si} – \text{O} \ldots\)) and organic side groups, commonly hydrocarbons, linked to the silicon atoms. This structure contributes to silicones’ low surface tension. The most common linear siloxane is polydimethylsiloxane (PDMS), whose chemical structure gives rise to unique properties: namely, the high bond energy (445 kJ/mol) of its \(\text{Si} – \text{O}\) bond allows for great freedom of rotation around bonds, which translates to both high chemical stability and high chain mobility. In addition, PMDS has high-temperature stability, is chemically inert and environmentally stable.

Silicone adhesives play an important role in medical industry applications due to their favorable chemical and mechanical properties, many of which derive from the unique nature of PMDS. An overview of the properties that contribute to silicone adhesives’ superior performance is presented below.

- Temperature stability: silicone adhesives are stable across a wide temperature range, from -100 °C to almost 300°C.
- Chemical stability: silicone adhesives efficiently resist both acidic and basic conditions and are stable in different solvents.
- Environmental stability: silicone adhesives are stable when exposed to oxygen, ultraviolet (UV) light and moisture.
- Flexibility: silicone adhesives adapt and conform to many substrates.
- Low surface tension at 24 mN/m: silicone adhesives easily adhere to surfaces.
- Low chemical/drug reactivity: silicone adhesives used for medical applications are “made” even more chemically inert in order to avoid any possible reaction with drugs/active compounds embedded in them. This is achieved by inserting a silane capping agent.
- High gas permeability: silicone adhesives exhibit excellent oxygen permeability and a high water vapor transmission rate (WVTR), making them excellent candidates for wound care applications.
- Low toxicity: silicone adhesives, as well as silicone elastomers, have been used in several medical applications with no reported toxicity.
3.7 Why Silicone Adhesives in Medical Applications?

Silicone adhesives fulfill several of the necessary requirements for medical applications. For example, they are generally biocompatible, as they are biologically inert, nontoxic and nonirritating. They can also be used effectively on skin and/or as transdermal drug delivery systems \(^{78,79}\). Silicone adhesives are especially preferred when contact on the skin is required due to their gentle skin adhesion properties as well as their flexibility and biocompatibility. Gentle skin adhesion results from the inherent softness and low surface tension of the silicone network, the latter of which provides adhesion and conformability to various skin types. These properties facilitate polymer chain mobility on the skin, but also into the uneven wounded skin, thereby creating a large, intimate contact area on the skin surface. In addition, since silicone adhesives can be removed from the skin without leaving any noticeable residue, they are considered atraumatic \(^{80–84}\).

Silicone adhesives possess excellent oxygen permeability and high WVTR, properties that are desirable in wound management as they make it possible to avoid maceration of the skin. Maceration, which is visible as softening and/or whitish skin discoloration, occurs when the skin is exposed to high amounts of liquid, such as sweat and/or wound exudates. In order to avoid maceration, skin adhesives must therefore allow moisture transmission at the skin-adhesive interface \(^{78,79}\). Despite its high WVTR, silicones possess inherent hydrophobicity, which can be problematic when consistent amounts of liquid need to be absorbed from a wound. If the amount of liquid produced by the skin and/or wound overcomes the absorption capacity of the adhesive, the latter will lose its adhesive properties due to rearrangement of the polymer chains and eventually fall off. Developing a new strategy to increase both the water absorption capability and permeability of silicone adhesives is therefore one of the main objectives of this PhD thesis.

3.8 Hydrosilylation Cured Silicone Adhesives

Hydrosilylation cured silicone adhesives have always drawn significant interest from the healthcare industry. The adhesives resulting from this type of cure chemistry are softer and possess more gentle skin adhesion compared to other silicone PSAs (standard silicone PSAs are cured via condensation of a PDMS silicone with MQ siloxane resin dispersion in a volatile solvent). They are considered low-peel-adhesion systems, and are required when dealing with very fragile skin in the setting of chronic wound management. Compared to traditional wound dressings, hydrosilylation cured silicone adhesives cause less pain and trauma upon removal, and do not damage the periwound skin \(^{85,86}\). These specific formulations are designed as two-component silicone adhesive premixes, usually called Part A and Part B; one component is a vinyl-functionalized PDMS, and the second is a hydride-functionalized PDMS. The cross-linking of the two is catalyzed by platinum (Pt), and the hydrosilylation reaction can occur at both room and elevated temperatures (see Figure 3.3) \(^{87}\).
In addition to imparting favorable chemical and mechanical properties to silicone adhesives for medical applications, hydrosilylation curing is a reliable preparation method for silicone elastomers/adhesives more generally. For example, because the reaction between the hydride and vinyl groups proceeds with high conversion and limited side reactions, it is also widely used in industrial applications. Nevertheless, challenges remain with respect to inhibition or poisoning of the Pt catalyst employed in the hydrosilylation reaction. Many substances, such as sulfur-, phosphorous- and nitrogen-containing compounds, inhibit hydrosilylation by forming competitive and irreversible complexes with the Pt, resulting in slower or unsuccessful curing. Such a scenario can be a problem if the goal is to incorporate pharmaceutical compounds into silicone adhesives in order to use them as drug delivery systems, limiting the number of drugs that are compatible with hydrosilylation cured silicone adhesives.

**Figure 3.3.** Schematic illustration of the platinum-catalyzed hydrosilylation curing between a vinyl-functionalized PDMS and a hydride-functionalized PDMS.
Chapter 3 – Principles of Adhesion and Adhesives

As discussed in Chapter 2, one of the major complications associated with chronic wounds is bacterial infection. A silicone adhesive that could prevent or treat bacterial infection would therefore be beneficial for chronic wound management. Therefore, a new strategy to allow the incorporation of an antiseptic drug, octenidine, into hydrosilylation cured silicone adhesives to create a novel antimicrobial adhesive is the final focus of this PhD thesis. The chemical structure of this drug possess two amino groups. As mentioned previously, nitrogen-containing compounds are inhibitors of the sensitive Pt catalyst used in the hydrosilylation reaction. The incorporation of octenidine into silicone adhesives has been achieved by cyclodextrins.

3.9 Cyclodextrins
Cyclodextrins deserve a note in this PhD dissertation, since their use is investigated as tool to cure silicone adhesives through hydrosilylation in the presence of a Pt-inhibiting molecule, octenidine, which will be discussed in Chapter 5.

Cyclodextrins (CDs) are cyclic oligosaccegharides consisting of (α-1,4)-linked α-D-glucopyranose units. They contain a lipophilic central cavity and a hydrophilic outer surface. Due to the chair conformation of the glucopyranose units, CDs are shaped like a truncated cone. The hydroxyl functions are orientated to the cone exterior, while the central cavity consists of the skeletal carbons and ethereal oxygens of the glucose residues. Such conformation leads to outer hydrophilicity and inner lipophilicity. In aqueous solutions CDs are able to form inclusion complexes with many drugs by taking up a drug molecule, or more frequently some lipophilic moiety of the molecule, into the central cavity. No covalent bonds are formed or broken during the complex formation and drug molecules in the complex are in rapid equilibrium with free molecules in the solution. The driving forces for the complex formation include release of enthalpy-rich water molecules from the cavity, electrostatic interactions, van der Waals interactions, hydrophobic interactions, hydrogen bonding, release of conformational strain and charge-transfer interactions. The most common type of CD complexes is the 1:1 CD:drug complex, where only one drug molecule forms a complex with one CD molecule (Figure 3.4):
Kc is the stability constant. If a drug molecule (D) associate with a CD molecule (CD) to form a complex (D-CD) in solution, Kc is expressed as:

\[ K_c = \frac{[D-CD]}{[D][CD]} \]  

where the square brackets refer to the concentration in solution of each component. Another common stoichiometry of CD:drug complexes is the 2:1. Such complex is formed when one additional CD molecule forms a complex with an existing 1:1 complex \(101^{–103}\).

Furthermore, CDs and CD complexes self-associate to form aggregate or micelle-like structures consisting of two to several hundred CD molecules and/or CD complexes \(^{99}\).
4. Glycerol-Silicone Adhesives with Improved Fluid Handling Properties

The following chapter is based on the article “Glycerol-silicone adhesives with excellent fluid handling and mechanical properties for advanced wound care applications”. It was available online June 17th 2020 and in print June 2020. Herein, a method to improve both the permeability and the water absorption of silicone adhesives is presented.

The article in its final accepted version can be seen in Appendix A, together with the Supplementary Information.

Contributions: Johannes Eiler, PhD Student at DTU Chemistry and Coloplast A/S – Adhesives, is the inventor of the sweat model. Daniel Bo Larsen, Scientist at Coloplast A/S, helped with setting the tack tests. Imaging data was collected at the Center for Advanced Bioimaging (CAB) at University of Copenhagen. All remaining work in this chapter, including analysis of the experimental data, was performed by Valeria Chiaula, with supervision from Piotr Mazurek, Anders Christian Nielsen and Anne Ladegaard Skov.

4.1 Introduction

Increased numbers of patients are affected by wounds and, in particular, chronic wounds\textsuperscript{104,105}, as a consequence of diabetes and other chronic diseases that may affect wound healing\textsuperscript{106}. To avoid chronic wounds and to promote faster healing, it is important to maintain a humid environment in the wound while at the same time ensure that the surrounding skin is not macerated due to presence of too much liquid (water, sweat, and exudate) in close contact with the wound\textsuperscript{107,108}. Currently, many adhesives are far too impermeable to avoid maceration over long periods, and therefore, as an example, holes are implemented into the adhesives to allow for moisture transport via larger microscopic or even macroscopic channels. However, these only help locally and maceration may still occur away from the holes. Also, the implemented holes may collapse over time and deplete. A more dense and homogeneous distribution of highly water conducting channels is therefore required for ideal wound healing.

Pressure sensitive adhesives (PSAs) constitute a widely used class of adhesive material in consumer products\textsuperscript{44,77}. For wound care applications, the PSAs must be soft and viscoelastic, yet solid, to adapt to human skin in a comfortable manner\textsuperscript{45}. Silicone adhesives are usually off-stoichiometric silicone elastomers that remain close to their gelation threshold (i.e. with a low cross-linking degree)\textsuperscript{59,109}, and within the field of advanced wound care, silicones are currently the preferred adhesive system due to their gentle skin adhesion properties\textsuperscript{80–82}. Their softness and low surface tension facilitate polymer chain mobility on and into the skin, thereby creating a large, intimate contact area on the uneven skin surface\textsuperscript{84}. In addition, silicone adhesives do not leave a significant residue on the skin when removed, and therefore they are considered atraumatic\textsuperscript{85}. 

To avoid maceration, a wound care adhesive should allow for effective moisture transmission at the skin-adhesive interface. Due to large mobility of the silicone polymer chains (silicone has a high free volume at room temperature), silicone adhesives have excellent oxygen permeability and a high water vapor transmission rate (WVTR) \(^{45,50}\), and therefore handle transport of gaseous substances well. However, due to their inherent hydrophobic nature, current silicone adhesive solutions are challenged when it comes to fluid handling, in that basic perspiration from the patient’s skin can cause the dressing to lose its adhesive properties and eventually fall off. Failure occurs if the amount of sweat produced by the patient’s skin is greater than the sum of absorption capacity and the permeability of the adhesive \(^{62,110-113}\).

To overcome the hydrophobicity of the silicone surface, grafting of hydrophilic moieties to the silicone surface has been investigated \(^{114-116}\). The resulting increase in water transport is initially large but over time the silicone depletes the hydrophilic surface due to the low surface energy of the hydrophobic silicone by absorbing the hydrophilic groups into the bulk of silicone \(^{117}\).

Two-phase glycerol-silicone hybrid elastomers which, depending on formulation, possess a bi-continuous or closed cell structure have been thoroughly described by Mazurek \textit{et al} \(^{118}\). They can be shaped as thin films, bulk elements and foams \(^{119}\). Both constituents furthermore are known to be biocompatible and non-toxic \(^{120-122}\). The glycerol-silicone composites are created in a simple manner by providing high shear forces to mixtures of glycerol and silicone prepolymer \(^{118}\). In this way, physically stable glycerol-in-silicone emulsions are formed which, upon cross-linking of the silicone phase, form free-standing two-phase elastomers. As reported previously, upon contact with an aqueous phase, the composites absorb significant amounts of water \(^{118,123,124}\).

The use of glycerol-silicone composites as skin adhesives has not been described before. Herein, we present a novel glycerol-silicone hybrid adhesive with improved fluid handling properties as a result of micrometer-sized glycerol droplets dispersed evenly throughout the silicone adhesive. We find that incorporating glycerol increases the water absorption and permeability of silicone adhesives, thereby making them potential candidates for use as wound care adhesives.

### 4.2 Experimental

#### 4.2.1 Materials

A commercially available two-part system (part A and part B) hydrosilylation-curing MG7-9900 soft silicone adhesive kit was purchased from DowDuPont Inc.\textsuperscript{TM}. Glycerol was kindly provided by Emmelev A/S, Denmark. Perylene (synthesis grade) and sulforhodamine B acid chloride (technical grade) were acquired from Sigma-Aldrich, Denmark. All the components were used as received. Polyethylene terephthalate (PET) and polyurethane (PU) backing films were provided by Mitsubishi Polyester Film (Germany) and by Coveris (UK), respectively. A fluorinated
Chapter 4 – Glycerol-Silicone Adhesives

ethylene propylene (FEP) release liner was purchased from Lohmann (UK). A UV-curable polymer film (MX5050) used to create the artificial skin was provided by Dupont (USA).

4.3 Methods

4.3.1 Sample Preparation
The two components of the commercial soft silicone adhesive kit were mixed in a 1:1 ratio by weight, as recommended by the manufacturer. Subsequently the desired amount of glycerol was added to the silicone adhesive premix. The abbreviation ‘phr’, used to describe glycerol content in all compositions, corresponds to glycerol weight per hundred parts of silicone adhesive. So, for example, 10 phr means that 10 g of glycerol was used per 100 g of the silicone adhesive premix. Samples name were formed using the GX pattern, where ‘G’ and ‘X’ stand for glycerol and glycerol phr added to silicone adhesive premix, respectively (for instance, G40 is 40 phr of glycerol). The mixtures were stirred for 2 min in two steps: 1 min by hand-mixing with a spatula and 1 min at 3500 rpm with a dual asymmetric centrifuge SpeedMixer DAC 150 FVZ-K (Germany). No additional degassing of the formulations was necessary. The obtained glycerol-in-silicone emulsions were coated at 23 mm/s onto a PET or PU backing film with commercial knives (with gap sizes of 0.4 mm or 0.8 mm) and an RK K Control Coater to obtain adhesives with thicknesses around 0.3 or 0.6 mm. The samples were subsequently cured at 80 ± 1°C for 1 h and then cut in a pre-defined shape. All samples were covered with an FEP release liner after coating, and before any measurement took place, this liner was removed. Adhesive thicknesses were then measured using a digital thickness gauge (Mitutoyo, Germany).

4.3.2 Morphology of Glycerol-Silicone Adhesives and Determination of Glycerol Surface Area per Volume of Adhesive
A Leica DM LB optical microscope was used to investigate the morphologies of the uncured samples, whilst a confocal Leica TCS SP5 X was used to analyse the morphology of cured composites. In order to demonstrate the distribution of glycerol droplets into silicone, we labelled each phase with different colour dyes. Sulforhodamine B and perylene were used to dye the glycerol and the silicone phases, respectively. To determine the glycerol surface area per volume of adhesive, glycerol spherical droplets in the formulation were measured in terms of their diameter by counting the droplets directly from microscopy pictures, using ImageJ software. The detailed calculations are reported in Supplementary Information in Appendix A.
4.3.3 Fluid Handling Capability of Adhesives

To measure the permeability of the adhesives, specimens of area (A) 10 cm$^2$ and thickness 0.3 mm were cut out and placed into Paddington chambers, which are the commonly used set-up for measurements of fluid handling capacity and permeability according to European Standard EN 13726-1 2002. Each chamber was closed with a lid when the experiments started. The test chambers with fixed samples and lids were weighed ($W_1$). Subsequently, 20 mL of saline test solution (8.298 g NaCl and 0.368 g CaCl$\cdot$(H$_2$O)$_2$ in 1 L of deionized water) was transferred to each chamber and the weights recorded ($W_2$). The assembled test chambers were closed and placed on a plastic tray inside a climatic test cabinet at 37 ± 1 °C and 15% RH. The water was in direct contact with the adhesives. After 24 h, the test chambers were removed from the climatic cabinet and left at room temperature for 30 min. After this time, the test chambers were weighed again ($W_3$). Five repetitions of the test were done for each compositions. Permeability, or WVTR, over 24 h was reported as:

$$\text{WVTR} \times \Delta t = \frac{(W_2 - W_3)}{A}$$

To determine the water absorption capability of the adhesives, specimens of area (A) 10 cm$^2$ and thickness 0.3 mm were weighed ($W_0$) and subsequently immersed in saline test solution for 24 h. After 24h, samples were thoroughly dried with absorbing paper to remove any residual water droplets from the surface and weighed again ($W_{24}$). Three repetitions of the test were run for each composition. The water absorption over 24 h was reported as:

$$\text{WA} \times \Delta t = \frac{(W_{24} - W_0)}{A}$$

4.3.4 Linear Viscoelastic Measurements

Linear viscoelastic (LVE) properties of glycerol-silicone adhesives were measured with a Discovery HR-2 Hybrid Rheometer (TA Instruments) using a parallel-plate geometry 20 mm in diameter. The instrument was set to a controlled strain mode ensured to be within the linear regime. Strain was set at 1%, and frequency sweeps were performed from 100 Hz to 0.01 Hz at 32 °C. Samples thicknesses were 0.6 mm. Measurements were done in triplicate for each composition.

4.3.5 Peel Tests on Stainless Steel Plates and Pig Skin

Samples with a thickness of 0.3 mm were cut in 25 mm x 100 mm rectangles. A TESA 4651 auxiliary tape was then cut in 25 mm wide strips, which in turn were glued to the adhesives. Each adhesive was carefully applied manually to a steel plate and/or pig skin. An automatic roll-down
laminating machine (applied pressure 2 kg and rolling speed 300 mm/min) designed for the purpose was used to minimize air inclusion between sample and substrate. Steel plates and/or pig skin with mounted adhesives were then equilibrated for 30 min in a test cabinet at 32 ± 1 °C. Subsequently, peel tests were performed using a Texture Analyser (TA) XT Plus (Micro Systems Ltd., UK). Peel rate and peel angle were set at 5 mm/s and 180°, respectively, for the adhesives mounted on steel plates. For the tests performed on pig skin, peel rate was 5, 1 and 0.1 mm/s, respectively. The peel angle was kept constant at 180°. Five measurements for each composition were performed and results were averaged.

4.3.6 Perspiration Simulator and Perspiration Experiments
The simulator consisted of an artificial skin membrane, mimicking human skin in terms of topography, water contact angle, and sweat pore distribution, was glued to a sweat reservoir. A sweat pore density of 100 cm$^{-2}$ was chosen to represent skin in the abdominal area. Dimensions of artificial skin were 25 mm x 40 mm. Adhesives for the experiments were cut to the same dimensions and then applied to the artificial skin with a defined pressure and over a set time. The reservoir was connected to a custom-made device for controlling the desired height of the water column and thus the desired pressure during the test. The tank was filled with a saline solution of 0.154 M NaCl. The height of the tank was set to achieve a pressure of around 2 kPa, which corresponds to typical pressures observed during perspiration. The tank was connected to the inlet of the reservoir through a tube and the sweat flow was controlled through a valve connected to a flow sensor (Elveflow, France). After 30 min, the sweat flow was stopped and adhesives were peeled off the artificial skin to determine the effect of perspiration on peel force. Peel tests were performed using an Instron 5943. Peel angle and peel rate were set at 90° and 5 mm/s. Three perspiration experiments followed by peel tests were run for each composition. As references, samples were contacted with the artificial skin for 30 min, with no exposure to saline composition, and subsequently peeled off.

4.3.7 Tack Tests
A modified version of the Loop Tack method (AST D6195-03) was used for testing. The loop was made of a rectangular strip of printing-paper, dimensions were 25 mm x 175 mm and it was closed with a 25 mm x 25 mm square of double-sided tape. The loop was then mounted in a clamp-fixture on an Instron 5543 and placed with a 2-4 mm gap between the loop and the adhesive. Adhesives were cut to dimensions of 25 mm x 100 mm and mounted on top of a T-shaped platform fixed in the lower grip of the Instron 5543. The loop was lowered until it completely covered the adhesive at a rate of at 5 mm/s, followed by immediate reversal at the same rate, until complete detachment from the sample and return to the initial position. The maximum peak and tack forces were
measured from the obtained force curve. Five measurements for each sample were performed and results were averaged.

4.4 Results and Discussion

4.4.1 Morphology of Glycerol-silicone Adhesives and Determination of Glycerol Surface Area per Volume of Adhesive

Glycerol-silicone adhesives were produced by applying high shear forces to the glycerol and adhesive premixes. Silicone constitutes the continuous phase with dispersed, discrete droplets of glycerol homogeneously distributed within. Confocal microscopy images of cross-sections of cured adhesives with varying content of glycerol are shown in Figure 4.1. Confocal image analysis of the resulting morphology shows that with increased loading of glycerol, the glycerol droplets become larger and more densely distributed despite identical mixing and curing conditions. This is in contrast to results for the previous studies of mixing glycerol into silicone elastomers, where the diameter of the droplet remained constant for a wide range of glycerol loadings undergoing the same mixing and curing procedures. However, the previously investigated elastomers also possess a significant fraction of silica fillers that are believed to stabilize the initial emulsions and thereby also the resulting material. In the current study, the silicone adhesive formulations are filler-free, therefore the stabilizing effect is missing. Furthermore, when glycerol loading increases, more droplets are generated during the emulsion preparation and, additionally, the space between the droplets decreases. Therefore, the possibility of droplets agglomeration increases, explaining the larger droplets observed for high-glycerol adhesives. The average droplet diameters as function of glycerol loading are shown in SI. To facilitate the understanding of the counterintuitive rheological behavior in the following sections, the surface area of the droplets is required. Knowing the diameter of a glycerol sphere \((D_i)\) and the glycerol volume fraction in a silicone adhesive \((\phi)\), the internal surface area \((\sum_i^N A_i)\) per volume of adhesive volume \((V_{tot})\) is calculated by means of simple geometry as:

\[
\frac{\sum_i^N A_i}{V_{tot}} = \frac{\varphi \sum_i^N A_i}{\sum_i^N V_i} = \frac{6 \varphi \sum_i^N D_i^2}{\sum_i^N D_i^3} \tag{12}
\]

since the volume of glycerol can be written as \(\sum_i^N V_i = \varphi V_{tot}\) and the diameter of glycerol spheres can be written as \(D_i = \sqrt[3]{\frac{6 V_i}{\pi}}\).

The estimated internal glycerol-silicone surface area per volume of adhesive was determined from averaging over 1,000 droplets. The achieved results are shown in Figure 4.2. The internal surface
Chapter 4 – Glycerol-Silicone Adhesives

area steadily increases until it reaches a maximum at 40 phr loading. Subsequently, the extra loading of glycerol no longer increases the internal surface area but rather results in significantly larger droplets - and thereby a reduction of the internal surface area despite the introduction of more glycerol.

Figure 4.1. Confocal microscopy images of cured glycerol-silicone adhesives. Higher glycerol amount results in thinner spacing between droplets and in larger droplet diameters. 10, 40 and 70 phr correspond to volume fraction of 7%, 23% and 35%, respectively.

Figure 4.2. Glycerol surface area per volume of adhesive determined from image analysis of confocal microscopy images.
4.4.2 Water Absorption and Permeability

For the glycerol-silicone adhesives, water absorption is an effect of building up osmotic pressure. As water moves down its osmotic potential gradient, it starts to fill the glycerol domains embedded in the silicone adhesive. It was previously shown that water absorption was shown to be more efficient both with respect to rate and total capacity at increasing glycerol loadings for glycerol-silicone elastomers, i.e. more densely cross-linked silicones than the adhesives. It is also known that the softer the silicone, i.e. reduced cross-linking density, the more water can potentially be absorbed by the formulations, as lower elastic stress has to be overcome to expand the glycerol domains. Results for water absorption and permeability over 24 h are presented in Figure 4.3 and a sketch of the water absorption mechanism is illustrated in Figure 4.4. The buildup of sweat at the skin-adhesive interface is unfavorable with respect to adhesion as well as it causes maceration. The glycerol-silicone elastomers allow for removal of the liquid at the interface due to the hygroscopic nature of glycerol. As expected, water absorption increased with increasing glycerol content. Specifically, water uptake increased up to 0.75 g/10 cm²/day for adhesives containing 50 phr of glycerol compared to the pristine silicone adhesive sample. However, it is surprising that the absorption of adhesives with 60 and 70 phr of glycerol did not increase further, but stabilized at similar level as the 50 phr adhesive. The reduced absorption level after 24 h observed for these samples can be explained by the determined glycerol surface areas per volume of adhesive, reported in Figure 4.2. As result of larger average droplet sizes in the higher-glycerol-loading formulations, the glycerol surface area per volume of adhesive did not increase further after 50 phr, but actually decreased for 60 and 70 phr adhesive samples. Hence, the available surface area of glycerol exposed to water during the water absorption experiments is smaller than the available surface area in 40 and 50 phr samples, thus explaining the lower absorption levels after 24 h. In other words, the interfacial area governs the rate of water uptake. Furthermore, since the 60 and 70 phr adhesives did not reach their final absorption capacity after 24 h, the recorded data is transient and this explains the deviation from the behavior of the silicone elastomers, where water uptake scales with loading of glycerol.

The permeability of glycerol-silicone adhesives increased in line with glycerol content as expected. Specifically, an increase of 230% for the 70 phr adhesive samples was observed compared to the pristine silicone sample.

In general, the overall enhancement of fluid handling capabilities of glycerol-silicone adhesives in a 24 hours period, facilitated by incorporating emulsified glycerol, was proved, with up to 50 times in water absorption and 3 times increase in permeability compared to the pristine silicone adhesive.
Figure 4.3. Water absorption and permeability of glycerol-silicone adhesives with different glycerol loadings measured at 37 °C and 15% RH over 24 h. A period of 24 hours is chosen as a representative time for a wound care adhesive. None of the glycerol-silicone adhesives has received their full absorption capacities in the given period due to the transient nature of the adhesives where they simultaneously transport water vapor through the material and water absorption in the glycerol.

Figure 4.4. Schematic illustration of the water absorption mechanism by glycerol droplets.
4.4.3 Linear Viscoelastic Properties of Glycerol-Silicone Adhesives

Figure 4.5A and 4.5B illustrate storage moduli (G’) and dissipation factors (tan δ = G’'/G’) as a function of frequency for adhesives with glycerol loadings from 0 to 70 phr. Data shows that the adhesives soften in their linear viscoelastic response (i.e. lower G’) to increasing glycerol content, as expected, due to the larger volume fraction of liquid. However, counterintuitively, tan δ decreases across the entire frequency range in line with increased loading of glycerol, thereby indicating that the elastic response compared to the viscous response increases as the samples contain more and more liquid. This can be explained by the elasticity of the cross-linked emulsions having two elastic components, namely the elasticity arising from silicone network and the internal interfacial energies, whereas glycerol does not contribute much to the viscous loss at the given temperature. The results thereby indicate that the interfacial energies constitute a major contribution to elasticity for the soft silicone adhesives.

Furthermore, from Figure 4.5B it can be seen that with increased glycerol loading the characteristic relaxation time (as identified by τ = 1/ω for the frequency for which d(tan δ)/dω = 0, where τ and ω are relaxation time and angular frequency, respectively) decreases. This indicates that - despite the less lossy nature of the adhesive with increased glycerol - the dynamics within the adhesive is speeded up at least a decade from 0 phr to 70 phr. This agrees well with higher mobility at the interfaces compared to the bulk properties.
4.4.4 Peel Force Analysis of Glycerol-Silicone Hybrid Adhesives on Stainless Steel Plates

Peel forces of adhesives from stainless steel plates and their failure modes were investigated. The results are summarized in Figure 4.6A. Initially, a sharp decrease in peel force for the G0 to G20 samples is observed, and then no significant variations in peel forces are detected for increased glycerol loadings up to 50 phr. To explain this behavior, first of all, the true thickness of adhesive layer in contact with the substrate must be considered. The thickness of the adhesive \( d \) can be related to the peel force \( F_{\text{peel}} \) via the following equation 59:

\[
\frac{F_{\text{peel}}}{dW} = g(tan \delta)_{\text{peel}}
\]

where \( W \) is the width of adhesive, \( G_0 \) is the zero-shear modulus and \( \omega_{\text{peel}} \) is the frequency of the peeling experiment. \( g \) is a function, most commonly in the form of \( g(x) = x \), and with this assumption the peel force per width of adhesive can be written:

\[
\frac{F_{\text{peel}}}{W} = dG_0 tan \delta_{\text{peel}}
\]

The true thickness of the adhesive layer instantaneously reduces when glycerol is introduced into the adhesive. This is due to the presence of discrete glycerol droplets, since the thickness of the contacting adhesive is no longer the thickness of the film but rather a distance closely related to the average thickness between droplets. This can explain the rapid drop in peel force from 0 to 10 phr. At the same time, at the peel frequency of \((5 \text{ mm s}^{-1} / 0.30 \text{ mm} = 17 \text{ s}^{-1})\) there is not much change in \( tan \delta \) or \( G_0 \) between 0 and 10 phr. Upon further increases in glycerol loading, the peel force remains constant within experimental uncertainty, due to a combination of no significant reduction in \( d \) and a small increase in \( G_0 \), caused by a stiffening effect from the increased number of droplets in the adhesive. Style et al 129,130 showed that surface tension acts to keep liquid inclusions spherical, thus opposing any applied stretch that would make liquid droplets elliptical.

All the compositions, from G0 to G50, exhibited adhesive failure at all frequencies. When glycerol loadings exceeded 50 phr, some instances of cohesive failure were observed, therefore the results were not included in the comparison. Cohesive failures at high loadings are addressed to the large fraction of liquid and thereby less adhesive to withhold the stresses and increased sensitivity to imperfections. As a result, the local stresses on some polymer strands become very high, and cause the adhesive to fail.
Chapter 4 – Glycerol-Silicone Adhesives

Figure 4.6. A) Peel average forces of silicone adhesives with various glycerol loadings on stainless steel plates. Peel force decreased in samples containing glycerol. No significant variations in peel forces were observed from G20 to G50. All compositions from G0 to G50 exhibited adhesive failure mode. B) Peel force vs. loss tangent measured at the peel frequency. Peel force decreases with tan δ from G0 to G20 samples, but remains constant within experimental uncertainty from G20 to G50 samples.

From Figure 4.6B it can also be seen that at low loadings the expected scaling of the peel force with tan δ prevails whereas for high loadings the scaling departs, probably due to the larger droplets and the resulting interplay between liquid stiffening and larger thickness of contact layer.

4.4.5 Peel Force Analysis of Glycerol-Silicone Adhesives on Pig Skin

Peel forces of glycerol-silicone adhesives from pig skin were investigated at three different peel rates. The results are presented in Figure 4.7 and show that the peel force decreases in line with the decreasing peel rate, indicating a correlation between mechanical response and peel velocity. This is in line with prior studies on PSAs \(^63,131–134\), that have shown that the relationship between peel force \((F)\) and peel velocity \((v)\) at the same peel angle can be described by:

\[
\frac{F}{b} = kv^n
\]  \hspace{1cm} (15)
Where \( b \) is the width of the adhesive, \( k \) is a constant that depends on the peel angle and the thickness of the PSA. \( n \) is a constant related to the intrinsic properties of the PSA \(^{131}\). From Figure 4.7 it is clear that – within experimental uncertainty – the peel forces of all the investigated adhesives, including the pristine silicone adhesive, behave identically with variation in peel rate. Therefore, it can be concluded that the intrinsic properties of silicone adhesives are maintained.

In addition, results show that overall there are no remarkable differences in peel forces from the G0 to G50 samples. This behavior is slightly in contrast to the peel forces from steel (Figure 4.6A), where a drop was observed from 0 to 10 phr reasoned to be due to introducing glycerol in the formulation, which reduces the true thickness of the adhesive layer in contact with the substrate. This deviation can be attributed to the competition between multiple factors. First, as discussed in the previous section, solid stiffening, as a result of glycerol inclusion, increases the experienced modulus. Secondly, as skin has an uneven surface compared to steel, the silicone chains can create a larger, intimate contact area with this substrate due to the high mobility of silicone chains at the interface.

All G0 to G50 compositions exhibited adhesive failure, and we observed instances of cohesion failure for adhesives containing 60 and 70 phr of glycerol. Therefore, these data were omitted.

**Figure 4.7.** Peel average forces of silicone adhesives with various glycerol amounts and at various peel rates from pig skin. The adhesive was pulled in the peel direction with an angle of 180° and with a speed of 5, 1 and 0.1 mm/s, respectively, at \( T = 32^\circ C \).
4.4.6 Perspiration Experiments and Adhesives’ Performance Characterization

The adhesives’ performance under high-perspiration conditions was evaluated using the perspiration simulator ideated by Eiler et al.\textsuperscript{135,136} This simulator recreates perspiration conditions similar to those occurring on human skin. Sweat glands typically exert pressure of approximately 2 kPa to generate perspiration rates up to 2 µL/cm\textsuperscript{2}/min\textsuperscript{125}. A simplified illustration of the simulator is shown in Figure 4.8A. From Figure 4.8B it can be seen that variations in peel forces between dry and wet samples were not remarkable. None of the compositions fell off the artificial skin during the experiments, with the single exception of G70. This suggests that almost all adhesives resist ≃ 2 kPa water pressure consistently. Moreover, glycerol-containing adhesives seem less affected (change from dry to sweat) by the simulated sweat pressure than G0. As discussed previously, as a consequence of fluid build-up in the interface skin-adhesive, adhesion failure may occur if the amount of liquid exceeds the absorbing capacity of an adhesive. Glycerol-silicone adhesives showed remarkable resistance during the sweat tests almost momentarily, indicating that glycerol may help remove eventual liquid-build-up at the adhesive-substrate interface, thus maintaining the adhesion level of dry adhesives as result of enhanced permeability.

\textbf{Figure 4.8.} A) Schematic illustration of the perspiration’ experiments’ set-up. The height of the tank containing simulated sweat was set to obtain a pressure of ≃ 2 kPa, resulting in a sweat rate of ≃ 2 µL/cm\textsuperscript{2}/min. Sweat time was set at 30 min. The adhesive was in contact with the artificial skin, which was glued to the sweat reservoir. B) Peel average forces of silicone adhesives with...
various glycerol amounts on artificial skin. Adhesives were pulled at an angle of 90° and a speed of 5 mm/s. Data revealed no loss of adhesive properties in wet samples compared to dry samples.

### 4.4.7 Tack Force Analysis of Glycerol-Silicone Hybrid Adhesives

The tackiness of glycerol-silicone hybrid adhesives was investigated. An illustration of the tack test set-up is shown in Figure 4.9A, and the results are shown in Figure 4.9B. No significant variations in tack forces were observed when increasing glycerol content in the silicone adhesives. Similarly to the peel force, we believe that the tack force is also affected by the solid stiffening effect. Furthermore, the paper used for the test consisted of high porosity between paper fibers such that the more mobile silicone chains can establish an immediate, large intimate contact area with the paper, as hypothesized in the case of the pig skin (*vide supra*). When glycerol loadings exceeded 50 phr, some instances of adhesive failure were observed, therefore data were omitted.

![Figure 4.9A](image1.png)

**Figure 4.9.** A) Sketch of the modified Loop Tack method (AST D6195-03). B) Tack average forces of silicone adhesives with various glycerol amounts. No significant variation in tack forces were observed from G0 to G50.
4.5 Conclusions

A novel glycerol-silicone adhesive was successfully prepared from speed-mixing mixtures of silicone adhesives and glycerol into stable emulsions. Upon cross-linking of the continuous silicone phase in the emulsions, glycerol-silicone adhesives were obtained, with glycerol embedded in the polymer in the form of discrete droplets. The fluid handling properties of glycerol-silicone adhesives were significantly increased by incorporating glycerol, and peel adhesion tests on stainless steel plates and pig skin revealed that the adhesives’ performance was not compromised by incorporating glycerol up to 50 phr. Above 50 phr of glycerol (corresponding to volume fractions of 28%) some instances of cohesive failure were observed. Additionally, perspiration simulation experiments revealed that glycerol-silicone adhesives showed remarkable resistance under harsh conditions. This indicates that glycerol helps removing eventual liquid build-up at the adhesive-substrate interface as a result of enhanced permeability (up to 3 times increased compared to pristine adhesives) and water absorption (up to 50 times compared to pristine adhesives). Lastly, the tackiness was not compromised by adding glycerol to adhesives at a loading up to 50 phr.

The very favorable properties of the prepared adhesives as well as the simplicity of the preparation scheme indicate a simple adhesive with properties partly governed by the used silicone adhesive system as well as the loading of glycerol into it.
Chapter 5 – Novel Antimicrobial Glycerol-Silicone Adhesives

5. Novel Antimicrobial Glycerol-Silicone Adhesives

This chapter is based on the manuscript for the article “Novel antimicrobial glycerol-silicone adhesives releasing octenidine incorporated via cyclodextrins”. It is the final draft submitted to the Journal “ACS Applied Materials & Interfaces”. Herein, a new method to include octenidine into glycerol-silicone adhesives is described. Specifically, a method to efficiently cure glycerol-silicone adhesives through hydrosilylation reaction in the presence of octenidine, which is an inhibitor of the Pt catalyst used in the reaction, is demonstrated.

The final submitted draft and the corresponding Supplementary Information can be found in Appendix B.

Contributions: Peter Jeppe Madsen, Senior Researcher at DTU Chemical Engineering, helped with carrying the NMR studies in the lab. Lotte Stoklund Jensen, Team Manager and Scientist at Coloplast A/S, helped with carrying the antimicrobial tests. Imaging data was collected at the Center for Advanced Bioimaging (CAB) at University of Copenhagen. All remaining work in this chapter, including analysis of the experimental data, was performed by Valeria Chiaula, with supervision from Piotr Mazurek, Anders Christian Nielsen and Anne Ladegaard Skov.

5.1 Introduction

Chronic wounds such as those often found in elderly and diabetic patients result from anomalies in cellular and molecular wound repair mechanisms. Specially designed materials are required in order to promote correct wound healing and closure in these patients, among which skin adhesives are of significant current research interest. Broadly, a skin adhesive must allow moisture transport to avoid skin maceration due to the presence of excess liquids (mainly sweat and exudate) while still maintaining a humid environment in the wound. In addition, the ability to reduce or prevent bacterial infections would be a valuable feature in skin adhesives for chronic wounds.

Our previous work thoroughly described a new glycerol-silicone hybrid adhesive with significantly improved fluid handling properties resulting from a hydrosilylation curing reaction. Hydrosilylation cured silicone elastomers are widely used in industry—e.g., as biomedical devices and medical skin adhesives. In general, hydrosilylation curing is a reliable method for preparing elastomers, as the reaction between the hydride and vinyl groups proceeds with high conversion and limited side reactions. Nevertheless, preventing the inhibition or poisoning of the platinum (Pt) catalyst used in the hydrosilylation curing reaction remains a challenge in certain cases. In general, all substances are potential inhibitors that complex Pt with an efficiency comparable to or higher than that of the vinyl groups, since hydrosilylation curing requires a labile Pt atom complexed to the vinyl group of the silicone. For example,
sulfur-, phosphorus- and nitrogen-containing compounds are all inhibitors, as they form competitive, irreversible complexes with Pt, resulting in slowed or unsuccessful curing \textsuperscript{95,97}.

The healthcare industry is particularly interested in silicone adhesives with topical antimicrobial properties. Among topical antimicrobials, silver has been known for decades to prevent microbial growth, and more recently has been incorporated directly into silicone dressings \textsuperscript{142–144}. Nevertheless, if in close contact to skin for an extended time, silver might be absorbed and lead to argyria, a local or systemic deposition of this metal in the skin itself \textsuperscript{145}. Chlorhexidine and triclosan are other commonly used antimicrobials. However, their extensive use is associated with antibiotic resistance and collateral effects, such as severe rashes and breathing difficulties \textsuperscript{30,146}. Alternative antimicrobial solutions are therefore needed.

Octenidine (Figure 5.1C) is a positively charged bis-pyridinamine with a broad spectrum of antibacterial (both towards gram positive and gram negative bacteria) and antifungal properties—as well as some antiviral ones—and is capable of inhibiting biofilm formation \textsuperscript{147,148}. In addition, octenidine has high biocompatibility, no known bacterial resistance, and is currently used as a wound cleansing agent and topical antiseptic \textsuperscript{149,150}. Because its chemical structure includes long alkyl chains and two amine groups, octenidine’s direct incorporation into silicone-based skin adhesives is not trivial, since the alkyl chains render it amphiphilic and the amine groups inhibit the hydrosilylation reaction. A new strategy to allow octenidine incorporation into silicone adhesives is thus required.

The use of glycerol-silicone elastomers as drug delivery systems was thoroughly described by Mazurek \textit{et al.} \textsuperscript{123}, who successfully demonstrated that glycerol domains act as reservoirs for small, hydrophilic molecules. Cyclodextrins are well known to have the ability to increase the aqueous solubility and stability of drugs with poor water solubility \textit{via} the formation of inclusion complexes \textsuperscript{99,151}. In addition, cyclodextrins are known to improve drugs’ chemical stability, and in some cases to improve their efficiency \textsuperscript{103,152}. Due to the chair conformation of the glucopyranose units, cyclodextrins attain the shape of a truncated cone (Figure 5.1B), resulting in a hydrophobic central cavity and a hydrophilic outer surface \textsuperscript{153}. This particular conformation allows cyclodextrins to host hydrophobic molecules inside their cavity, improving their aqueous solubility.

In this work, we describe a new method for incorporating octenidine into glycerol-silicone adhesives \textit{via} cyclodextrins. Specifically, we demonstrate a method for efficiently curing glycerol-silicone hybrid adhesives through hydrosilylation in the presence of octenidine via the formation of inclusion complexes, as demonstrated by ROESY spectroscopy. We find that cyclodextrins suppress the interference of octenidine with the Pt catalyst. We further demonstrate these
adhesives’ ability to release octenidine, enabling the preparation of silicone adhesives with antimicrobial properties.

**Figure 5.1.** A) Chemical structures of the hosts β-cyclodextrin and (2-hydroxypropyl)-β-cyclodextrin. B) The truncated cone shape of cyclodextrins. C) Chemical structure of the guest molecule octenidine.

### 5.2 Experimental

#### 5.2.1 Materials

A commercially available, two-part system (part A and part B) hydrosilylation curing soft silicone adhesive kit was used (MG7-9900 DowDuPont Inc. ™). Glycerol was provided by Emmelev A/S (DK). β-cyclodextrin (βCD), (2-hydroxypropyl)-β-cyclodextrin (HPβCD), perylene (synthesis grade) and sulforhodamine B acid chloride (technical grade) were acquired from Sigma-Aldrich (DK). Octenidine dihydrochloride (Oct) was purchased from Dishman Group (UK). *P. Aeruginosa* (ATCC 27853) and *E. Coli* (ATCC 53498) bacteria strains were purchased from Miclev (SE). Lecithin was purchased from VWR Chemicals (DK). Coloplast A/S (US) provided commercial products containing silver (Mepitel Ag). Polyethylene terephthalate (PET) and polyurethane (PU) backing films were purchased from Mitsubishi Polyester Film (DE) and Coveris (UK),
respectively. A fluorinated ethylene propylene (FEP) release liner was purchased from Lohmann (UK). All components were used as received.

5.3 Methods

5.3.1 Sample Preparation
The two parts of the commercial soft silicone adhesive kit were weighed off in a 1:1 ratio, according to the manufacturer’s instructions. The desired amount of glycerol was subsequently added to the silicone adhesive premix. The abbreviation ‘phr’, used to describe glycerol content in all compositions, corresponds to glycerol weight per hundred parts of silicone adhesive: e.g., 20 phr means that 20 g of glycerol was used per 100 g of silicone adhesive premix.

For samples containing cyclodextrins (CDs) and octenidine (Oct), the mass of Oct was set at 1 wt.% of the combined mass of adhesive premix and glycerol in all experiments. This ratio was chosen in agreement with Coloplast A/S, with the goal of having a moderate amount of Oct in the final formulation. The amount of CDs was adjusted according to the desired CDs:Oct molar ratio; mixtures were prepared in molar ratios ranging from 0.25 to 4, and dissolved in glycerol at 80 °C using magnetic stirring until clear solutions were obtained. The molar ratio $r$ is defined as:

$$r = \frac{n(\text{CD})}{n(\text{Oct})}$$

(16)

The desired amount of glycerol containing CDs:Oct mixture was subsequently added to the silicone adhesive premix. Sample names were formed using the patterns GX_Y, where ‘G’ and ‘X’ stand for glycerol and glycerol phr, respectively. ‘Y’ accounts for various parameters discussed in the following sections. Occasionally, ‘Y’ will be followed by a number, which stands for the molar ratio between CDs and Oct. A full description of all investigated samples can be found in Table 1 in the Supplementary Information (Appendix B).

The mixtures (silicone and glycerol, or silicone and glycerol containing CDs:Oct) were stirred for a total of 2 min: 1 min by hand-mixing with a spatula, followed by 1 min at 3500 rpm with a dual asymmetric centrifuge SpeedMixer DAC 150 FVZ-K (DE). No additional degassing of the formulations was necessary. The obtained glycerol-in-silicone emulsions were coated onto a PET backing film with a commercial knife (gap size of 0.4 mm) and a RK K Control Coater with a speed of 23 mm/s to obtain adhesives approximately 0.3 mm thick. The samples were subsequently cured at 80 ± 1°C for 1 h. All samples were covered with an FEP release liner after coating; this
liner was removed before any measurement took place. Adhesive thicknesses were measured prior testing between the two liners using a Mitutoyo digital thickness gauge (DE).

5.3.2 Curing Profiles of Glycerol-Silicone Adhesives and Linear Viscoelastic Measurements
Curing profiles of glycerol-silicone adhesives containing different CDs:Oct molar ratios were obtained by time sweep tests at 80 °C for 10 min on a controlled stress-strain ARES G2 rheometer (TA Instruments), using a parallel plate geometry 25 mm in diameter. The instrument was set to a controlled strain mode ensured to be within the linear regime. Frequency and strain were set at 1 Hz and 2 %, respectively. The gap between the plates was set to approximately 1 mm. Frequency sweeps were subsequently performed on the cured adhesives from 100 to 0.1 Hz at 32 °C to evaluate the linear viscoelastic properties of the cured adhesives.

5.3.3 Morphology of Glycerol-Silicone Adhesives
A Leica TCS SP5 X confocal microscope was used to investigate the morphology of cured composites. The composites were labelled with differently colored dyes in the manufacturing process: sulforhodamine B (0.1 wt.% relative to glycerol) for the glycerol phase, and perylene (10 µL of a perylene solution in isopropanol 2.53 mg/mL) for the silicone phase. To determine the average size distribution of the spherical glycerol droplets in the formulations, droplet diameters were measured by counting the droplets directly from microscopy pictures using ImageJ software.

5.3.4 NMR Studies
For NMR studies, HPβCD:Oct samples (r = 2) were dissolved in D₂O in a concentration of 20 mg/mL. All NMR spectra were acquired using a Bruker 300 MHz spectrometer at 293 K. For 1D ¹H NMR, 16 to 128 scans were collected. 2D Rotating frame Overhauser Effect SpectroscopY (ROESY) spectra were collected using a mixing time of 200 ms for detection of intermolecular nuclear overhauser effects (NOEs). 16 scans were collected for each spectrum. Data were analyzed using TopSpin version 3.5 pl 7 from Bruker. The ¹H NMR prediction software package in ChemOffice 2016 was used as an aid in assigning peaks.

5.3.5 Release Profiles of Glycerol-Silicone Adhesives
Oct release profiles from glycerol-silicone adhesives were obtained by immersing specimens containing various amounts of glycerol in deionized water. Measurements were performed at room temperature. Oct release was monitored by measuring the changes in Oct concentration of the
aqueous solution. A UV-vis spectrophotometer POLARstar Omega microplate reader (BMG LabTech) was used for the tests, and measurements were translated into concentrations using a calibration curve for aqueous HPβCD:Oct solutions. Oct quantification was performed at 280 nm (CDs did not show any absorbance peak in the UV-vis spectrum).

### 5.3.6 Antimicrobial Properties of Adhesives

Antimicrobial tests on glycerol-silicone adhesives containing HPβCD:Oct mixtures ($r = 2$) were performed using a modified version of the ISO22196 method. *P. Aeruginosa* (ATCC 27853) and *E. Coli* (ATCC 53498) bacteria strains were chosen for the tests and grown in a 0.9 wt.% NaCl solution. 200 µL of bacteria-containing solution was then placed on the bottom of a cell culture plate, and discs of cured adhesive (diameter 0.34 mm, thickness 0.3 mm) were put in contact with the liquid. Samples without HPβCD:Oct and a commercial product containing silver, Mepitel Ag, were used as controls. Tests were run in triplicate for each sample. Samples in direct contact with bacteria solutions were allowed to incubate for 24 h in a humid environment. After incubation, the samples were washed with 1.8 mL of 2 wt.% lecithin solution to neutralize Oct activity (according to the US Pharmacopeia). Samples of the liquid were then plated onto agar, incubated for 18-26 h at 35 °C, and CFU (colony forming units) were counted manually. Microbial concentrations were determined using a Biochrom WPA CO8000 Cell Density Meter. The reduction of microorganisms relative to initial concentrations was calculated and expressed in terms of ‘Log$_{10}$ CFU’. A description of the expressions to determine ‘Log$_{10}$ CFU’ is provided in the Supplementary Information.

### 5.4 Results and Discussion

#### 5.4.1 Investigation of The Best Molar Ratio CDs:Oct through The Evaluation of The Curing Profiles of Glycerol-Silicone Adhesives

Because Oct contains two amine groups (*Figure 5.1C*), it is an inhibitor of the Pt catalyst involved in hydrosilylation curing. Thus, if Oct is added directly to the silicone adhesive premix, curing does not proceed beyond gelation; in other words, crosslinking does not occur. A novel synthesis strategy is therefore needed that does not include toxic components, such as the less sensitive tin catalyst. One possibility is to add Oct at a different phase than the Pt catalyst, which is possible with glycerol-silicone adhesives. However, even if Oct is predominantly in the glycerol phase, its presence at the glycerol-silicone interface inhibits the curing of the silicone phase. For this reason, we used CDs to screen the Oct from the Pt. Two different CDs were investigated here: βCD and HPβCD (*Figure 5.1A*). The influence of CDs:Oct ratio on gelation time, which measures the
transition from liquid to solid, and elastic modulus after the cross-over point—i.e., after full cross-linking—were evaluated to find the optimal concentration of CDs in the system.

Glycerol-silicone adhesives’ gelation time and elastic modulus after curing are reported in Figure 5.2 (A-B) as a function of CDs:Oct ratio. The samples are compared to the corresponding complex-free compositions, i.e., with no CDs or Oct. The curing profiles of pure glycerol-silicone adhesives are shown in Figure S1 (Supplementary Information). As expected, the pure glycerol-silicone adhesives have different gelation times due to their different volume fractions of elastically active material. The pure silicone adhesive reaches gelation in 100 s, and gelation time is shortened when the glycerol content is increased. This is due to the fact glycerol droplets in the soft silicone adhesive premixes contribute to elasticity in the liquid state due to their interfacial energies, introducing a so-called solid stiffening effect. In principle, the larger the number and smaller the size of the glycerol droplets, the greater the elastic contribution. The cross-over over G’ and G”, which is commonly used as measures of gelation time, is reached before the true gelation of the silicone phase. G50 is made from a different batch of silicone adhesive, and the gelation time is therefore not consistent with the remaining data. An even lower gelation time would be expected if these samples were from the same adhesive batch.

Gelation times were found to decrease and elastic moduli to increase with increasing CDs:Oct ratio (Figure 5.2, A-B). When \( r = 2 \) and 4, gelation times and elastic moduli are comparable to or higher than those of the corresponding complex-free compositions. In particular, the elastic modulus of G20 increases from approximately 4000 Pa to over 5000 Pa when \( r = 2 \) and 4 (Figure 5.2B). Oct amounts are always 1 wt.% of overall mass. The mass of silicone decreases from G20 to G50 due to dilution with glycerol, but the Pt:silicone ratio remains constant for all compositions. However, this means that the Pt:Oct ratio is lower in compositions with higher glycerol content, which also have increased surface areas (the effect of glycerol surface area on mechanical properties is discussed in detail in section 3.3). HPβCD allows for the formation of CDs:Oct complexes with \( r \) up to 4, while βCD only allows complex formation for \( r \) up to 1 due to its lower solubility in glycerol compared to HPβCD. As Figure 5.2B shows, higher CDs:Oct ratios allow adhesives to reach elastic moduli comparable to those of the corresponding reference samples. Importantly, the elastic moduli of adhesives containing CDs:Oct ratios of 2 and 4 are comparable. This indicates that Pt inhibition is sufficiently suppressed at the lower ratio to ensure efficient cross-linking. Further increasing CDs content only changes the apparent gelation time due to the higher initial G’ of the premixes. To better understand the interaction between CDs and Oct at one of the favorable ratios—which, as mentioned previously, can only be achieved with HPβCD—a model NMR study of the system HPβCD:Oct with \( r = 2 \) was conducting using ROESY spectroscopy.
Figure 5.2. Investigation of the optimum CDs:Oct ratio through evaluation of gelation times and elastic moduli after full cross-linking. Measurements were conducted in the linear viscoelastic regime at 2% strain. All data was obtained from the curing profiles at 80 °C at a frequency of 2 Hz. A) Gelation times of glycerol-silicone adhesives as a function of CDs:Oct molar ratio. Horizontal lines correspond to gelation times of the complex-free reference compositions. B) Elastic moduli of glycerol-silicone adhesives as a function of CDs:Oct molar ratio and as a function of glycerol amount. Horizontal lines correspond to the elastic moduli of the reference compositions.

5.4.2 2D ROESY of HPβCD:Oct Complexes

Guest-host complexes between CDs and various guest molecules are examined using spectroscopic techniques such as NMR, which enable determination of the complexation constant and complex stoichiometry. However, the characterization of HPβCD:Oct complexes is potentially more complicated than that of other CDs:drug systems for several reasons: in order to suppress chemical shift effects from surfactant micellization, complex formation should ideally be analyzed below the critical micelle concentration (CMC), which is reported to be 3.79 mM for Oct. Due to NMR’s relatively low sensitivity, however, getting reliable measurements at such low concentrations requires a specific instrumental setup. In addition, there are reports that structurally similar gemini surfactants may form complexes with either one or two CDs, which would invalidate the use of the common Job’s plot for determining complex stoichiometry. More importantly, NMR studies of HPβCD are complicated by the fact that this molecule consists of a number of closely related isomers, which gives the resulting spectrum relatively broad features rather than well-defined sharp peaks.
Despite these complications, NMR was used to provide further details on the complexation between Oct and HPβCD in deuterated water (D2O). Initially, 1D 1H NMR and 2D COSY spectra were acquired separately for Oct and HPβCD (Figure 5.3, A-B). As reported, the 1H NMR spectrum of HPβCD exhibits several broad features between 3 and 4.5 ppm that do not allow for the exact assignment of individual protons.\textsuperscript{158} On the other hand, the 1D 1H NMR 2D COSY spectra of HPβCD:Oct in D2O allow full assignment of several protons for this compound (Figure 5.3B). In particular, both the aromatic protons and methylene protons α, β and ω to the nitrogen atoms can be assigned based on the combination of COSY, comparison to known compounds, and chemical prediction software. The assigned structure is given in Figure 5.3A.

The complexation between Oct and HPβCD was investigated using ROESY spectroscopy, a technique which exploits the nuclear overhauser effect (NOE) to detect through-space interactions between protons.\textsuperscript{159} The signal intensity scales with distance to the minus sixth (r\textsuperscript{-6}), and is therefore highly sensitive to the average distance between protons. In practice, however, distances above 4 Å do not give rise to any signal.\textsuperscript{154} Figure 5.3 (C-D) shows the ROESY spectrum of a HPβCD:Oct mixture with \( r = 2 \) in blue. This is superimposed on ROESY spectra of Oct (red) and HPβCD (black) in order to visualize additional signals in the mixture, indicating little distance between the two molecules.

Due to the broad signals that HPβCD generates, it is impossible to determine exactly which protons in the CD interact with Oct—i.e., whether the interaction is associated with cavity protons or external protons—limiting the possibility of exactly elucidating the complex structure. However, several conclusions can be drawn from the highlighted interaction regions in Figure 5.3 (C-D). In particular, protons a (region III), g (region IV) and i (region II) show greater interaction with HPβCD than protons l (region V, compare with region IV) and j (region I, compare with region II). Protons a and g are assigned to the terminal chains and protons i are ortho to the terminal chain, whereas protons l are assigned to the central chain and protons j are ortho to the polar pyridinium group. These results indicate that the terminal chains are particularly associated with the hydrophobic HPβCD cavity and that the aromatic ring constitutes the interface with the exterior, with the charged group being stabilized by the more polar environment. These findings are consistent with reports on complexes between structurally related gemini bis-(dodecyl dimethylammonium)diethyl dibromide surfactants and β-CDs.\textsuperscript{156} Due to the lack of fine structure in the spectral features of HPβCD, the ROESY spectrum cannot determine whether one or two HPβCDs complex to the Oct. However, previous work on related gemini complexes has indicated that complexes with both one and two CDs are possible, corresponding to one or both terminal chains embedded in the hydrophobic part of the CD.\textsuperscript{156} Complexes containing four β-CDs were also reported for a naphthalene-containing cationic gemini surfactant.\textsuperscript{160}

While elucidating the exact complex structure is beyond the scope of this work, the ROESY spectra do clearly indicate that Oct’s aniline groups interact strongly with the HPβCD. This interaction should suppress competitive complexation with the Pt catalyst, thereby suppressing inhibition of the polymerization process. Importantly, however, this argument is only valid if the HPβCD:Oct mixture has a similar structure in glycerol. Unfortunately, acquisition of high-quality ROESY spectra in glycerol was not feasible due to the high viscosity of this solvent combined with a
significant overlap between residual solvent signal and HPβCD. However, based on the observation that the solubility of Oct in glycerol is significantly increased in the presence of HPβCD, as well as the results from the curing experiments described in Figure 5.2 (A-B), it can be assumed that similar complexation occurs in this solvent.

Figure 5.3. Characterisation of HPβCD:Oct 2:1 mixture by 1H NMR. A) Assigned structure of Oct. B) 1H NMR spectrum of HPβCD:Oct \((r = 2)\) mixture in D2O. C) Enlarged region of ROESY spectrum emphasizing through-space (NOE) interaction between aromatic Oct signals and cyclodextrin. D) Enlarged region of ROESY spectrum emphasizing through-space.

5.4.3 Evaluation of The Linear Viscoelastic Properties of Glycerol-Silicone Adhesives Containing CDs:Oct Mixtures
To investigate how the incorporation of CDs:Oct into glycerol-silicone adhesives affects their mechanical behavior, shear rheology in the linear regime was performed. The full spectra of storage moduli \((G')\) and viscous moduli \((G'')\) are shown in Figures S2 and S3 in the Supplementary Information. Dissipation factors \((\tan \delta = G''/G')\) are shown in Figure 5.4 (A-D) as a function of both CDs:Oct ratio and glycerol content (as a reference).
Chapter 5 – Novel Antimicrobial Glycerol-Silicone Adhesives

Figure 5.4. Linear viscoelastic properties of adhesives. Measurements were conducted with controlled strain at 2% and frequency sweeps from 100 Hz to 0.1 Hz at T = 32 °C. A) Tan δ of glycerol-silicone adhesives containing 20, 40 and 50 phr, respectively, compared to a pristine silicone adhesive sample. B-D) Tan δ of G20, G40, and G50 adhesives, respectively, containing CDs:Oct mixture with r ranging from 0.25 to 4.

Counterintuitively, Figure 5.4A shows that tan δ decreases across the entire frequency range when liquid content increases. In other words, the composites become more solid with increased liquid content. Such behavior has previously been observed for glycerol-silicone adhesives with increasing glycerol content,138 and can be explained by the fact that the cross-linked emulsions have two distinct elastic components: the elasticity arising from the silicone network itself, and the interfacial energy between the two phases. Style et al. and the extended Eshelby theory previously described this so-called solid-stiffening effect caused by the glycerol droplets in soft silicone elastomers. They demonstrated that surface tension helps to keep liquid inclusions spherical, opposing any applied force that would make them elliptical.129,130 Furthermore, the
mechanical response of an isolated liquid inclusion depends on its size. In particular, when comparing two soft elastomers with the same interfacial area, the one with smaller droplets is the stiffer of the two. According to the extended Eshelby theory, the length $l$ and the width $w$ of a stretched droplet embedded in an elastic solid can be calculated via the equations given below\textsuperscript{129,161–163}:

\begin{align}
  l &= 2R \left[ 1 + \frac{5(2\varepsilon_1 - \varepsilon_2)}{6 + 15 \frac{\gamma}{ER}} \right] \\
  w &= 2R \left[ 1 + \frac{5(2\varepsilon_2 - \varepsilon_1)}{6 + 15 \frac{\gamma}{ER}} \right]
\end{align}

Where $R$ is the radius of the droplet, $\varepsilon_1$ and $\varepsilon_2$ are the applied far-field plane-stress boundary conditions for which $\varepsilon = \varepsilon^\infty$, $\varepsilon_1 = \left( \varepsilon_x^\infty + \nu \varepsilon_y^\infty \right) \frac{1}{1 - \nu^2}$ and $\varepsilon_2 = \left( \varepsilon_y^\infty + \nu \varepsilon_x^\infty \right) \frac{1}{1 - \nu^2}$, $x$ and $y$ are the strain directions, and $\nu$ is the Poisson’s ratio; $\gamma$ is the surface tension of the droplet and $E$ is the Young’s modulus of the solid. If $\gamma/ER \gg 1$, the effect of the surface tension which keeps the droplets spherical is predominant. The effect of CDs incorporated into glycerol-silicone adhesives is investigated further in Figure 5.4 (B-D). A higher elastic response—i.e. a lower tan $\delta$—is observed for adhesives containing HPβCD:Oct mixtures with $r > 1$, indicating that a change in the interfacial energies has occurred. To investigate whether the presence of HPβCD affects the size of the glycerol droplets, adhesives’ morphology was analyzed. Confocal microscopy images of cross-sections of cured adhesives containing a HPβCD:Oct mixture with $r = 2$, the relative internal glycerol surface area per adhesive volume, and tan $\delta$ (measured at 1 Hz) are shown in Figure 5.5 (A-C). Confocal image analysis confirms that the average droplet diameter decreases for samples containing HPβCD:Oct compared to their pure counterparts, resulting in a greater glycerol surface area per volume (Figure 5.5B). This is not surprising, as CDs are known to cause a stabilizing effect.
Chapter 5 – Novel Antimicrobial Glycerol-Silicone Adhesives

effect in emulsions. In addition, adhesives containing HPβCD possess lower tan δ compared to pure compositions (Figure 5.5C), most likely due to their increased interfacial area.

Figure 5.5. A) Confocal microscopy pictures of cured glycerol-silicone adhesives without (top) and with (bottom) HPβCD:Oct mixtures. All compositions with HPβCD:Oct contain 1 wt.% of Oct and \( r \) of 2. Scale bars correspond to 100 µm. B) Glycerol surface area per adhesive volume with and without HPβCD:Oct \( (r = 2) \) as a function of glycerol loading. C) Tan δ at 1 Hz of adhesives with and without HPβCD:Oct \( (r = 2) \) as a function of glycerol loading. Measurements were conducted with controlled strain of 2% at 32 °C.

To better understand how interfacial energies affect elasticity, we further analyzed the adhesives’ dynamics. The characteristic frequency, \( \omega_{\text{max}} \), at which \( \frac{d}{d\omega} (\tan \delta) = 0 \), is shown for pure glycerol-silicone adhesives and for drug-containing ones in Figures 5.6A and 5.6B, respectively. For pure glycerol-silicone adhesives, \( \omega_{\text{max}} \) increases in correlation to glycerol loading. In other words, the relaxation dynamics within the adhesive speed up when glycerol loading increases, while overall elasticity is also increased. Such behavior contradicts classical rubber elasticity theories in which dynamics slow down with increasing elasticity, emphasizing the importance of interfacial contributions to elasticity for these very soft materials. Indeed, these findings indicate that interfacial energies contribute significantly to the higher mobility observed at the glycerol-silicone interface compared to in the adhesive bulk. The characteristic frequency is not affected in the same manner for adhesives containing CDs:Oct mixtures, and remains constant for G40 and
G50 regardless of CDs content (Figure 5.6B). On the other hand, a drop in characteristic frequency is observed for G20 compositions with high CDs content, indicating that the CDs interact with the glycerol-silicone interface, either by changing the interfacial energy or by physically hindering free motion of the polymers at the interface. To better understand the influence of interfacial energies on adhesive elasticity, as well as how these energies change when CDs are introduced, the Maxwell relaxation time, $\tau_{\text{max}}$, can be used. The Maxwell model defines the characteristic time by defining $\tan \delta_{\text{max}}$ as 166:

$$\tan \delta_{\text{max}} = \frac{1}{\omega_{\text{max}} \tau_{\text{max}}}$$

Where $\tan \delta_{\text{max}}$ and $\omega_{\text{max}}$ are determined as described earlier, and $\tau_{\text{max}}$ is determined and plotted against surface area per volume in Figure 5.6 (C-D). While $\tau_{\text{max}}$ scales linearly with surface area per volume for pure glycerol-silicone adhesives (Figure 5.6C), the same linearity is not achieved for compositions containing CDs:Oct mixtures (Figure 5.6D), further suggesting that CDs and/or drugs interact with the interface. Since curing of the silicone adhesive was made possible by the efficient screening described previously, it must be the CDs that interact with the interface to reduce interfacial energies, also leading to the smaller elastic contribution observed for the samples, particularly the adhesives with HPβCD (Figure 5.2B).
5.4.4 Release profiles of Oct from glycerol-silicone adhesives and antimicrobial activity

As reported previously, glycerol-silicone composites can absorb significant amounts of water while simultaneously releasing glycerol upon contact with an aqueous phase. It is therefore expected that substances incorporated into glycerol domains will be released from the matrix, as glycerol domains act as reservoirs for these substances. Release profiles of Oct complexed with HPβCD at a ratio of $r = 2$ from glycerol-silicone adhesives with different glycerol contents are shown in Figure 5.7A. The corresponding release rates were plotted against glycerol content in Figure 5.7B. The results indicate that Oct is released faster from adhesives with higher glycerol content, in agreement with previously published findings for elastomers. Adhesives were
subsequently tested for antimicrobial activity against P. Aeruginosa and E. Coli bacteria strains, both of which are common wound pathogens. Bacterial colony growth on agar plates is shown in Figure 5.7 (C-D). While large bacterial colonies were present for both the pristine G50 sample and the commercial sample containing silver, Mepitel Ag, no colonies were visible for G50 samples containing HPβCD:Oct with $r = 2$. For the modified G50 samples, the reduction of microorganisms relative to their initial amount, expressed as ‘Log$_{10}$ CFU’, was 6 for P. Aeruginosa and 5 for E. Coli, indicating fully antimicrobial activity against both bacteria strains. No antimicrobial activity was observed for G20 samples loaded with Oct (data not shown), suggesting that the G20 samples did not achieve the minimum release rate required to efficiently kill the given bacteria.
Figure 5.3. A) Oct release profiles for G20, G40 and G50 glycerol-silicone adhesives with HPβCD:Oct ratio equal to 2. B) Release rate dependence on glycerol content. C-D) Bacteriological results of ISO2219 test and ‘Log₁₀CFU’ of the commercial samples and G50_Oct 1 wt.% (HPβCD:Oct with \( r = 2 \)), respectively. The adhesive samples were in direct contact with 200 µL of bacteria solutions containing \textit{P. Aeruginosa} and \textit{E. Coli}, respectively, for 24 h. Visible colonies appeared on both G50 samples without Oct and the commercial samples exposed to bacteria for 24 h after the liquid samples were plated onto agar. No colonies were visible after bacteria exposure of G50_Oct 1 wt. % (HPβCD:Oct with \( r = 2 \)).

5.5 Conclusions

We developed a novel antimicrobial glycerol-silicone adhesive capable of releasing Oct via CDs. Oct incorporation was achieved via CDs through formation of an inclusion complex with the drug. Rheological characterization of glycerol-silicone adhesives with varying CDs:Oct ratios showed
that HPβCD:Oct complexes with a ratio > 1 allowed incorporation of 1 wt.% of Oct without compromising adhesives’ mechanical properties. The interaction between HPβCD and Oct via an inclusion complex was further characterized and confirmed using ROESY spectroscopy. Finally, we demonstrated the possibility of releasing Oct from glycerol-silicone adhesives, and showed that a minimum release rate, obtained in G50 samples, is required to kill bacteria. Fully antimicrobial activity against *P. Aeruginosa* and *E. Coli* was achieved through G50 samples containing HPβCD:Oct in a molar ratio equal to 2.

Due to the favorable properties they display, together with their relatively simple preparation process, glycerol-silicone adhesives with Oct incorporated *via* CDs should be considered potential candidates for advanced wound care applications, in which it is necessary to both effectively promote wound healing and prevent bacterial infection.
6. Conclusion and Outlook

6.1 Conclusions
This PhD thesis aimed to develop new, industrially relevant silicone adhesives with improved fluid handling properties by investigating the use of glycerol-silicone composites as skin adhesives.

In the first part of this project, various amounts of glycerol were incorporated into the silicone adhesive matrix. The direct mixing of two virtually immiscible liquids, glycerol and silicone, formed relatively stable “glycerol-in-silicone” emulsions upon exposure to sufficiently high shear forces. The free-standing emulsions obtained were then coated and cross-linked via hydrosilylation into the shape of thin adhesive films. The incorporation of glycerol into silicone was intended to enhance both water absorption and permeability while maintaining the required adhesive properties, such as peel and tack. The amount of glycerol incorporated into silicone varied from 10 to 70 phr, 70 phr being the maximum amount of glycerol that it was possible to incorporate into silicone without severely compromising emulsion stability. The glycerol-silicone adhesives were shown to possess significantly increased water absorption and permeability compared to a pristine silicone adhesive sample. Specifically, the water absorption increased up to 50-fold compared to the sample, while the permeability increased up to 3-fold. In addition, water absorption capability was observed to increase in correlation with increased glycerol surface area per adhesive volume.

To investigate the effect of glycerol loadings on fundamental adhesive properties, peel and tack tests were performed. Peel tests from two different substrates, stainless steel and pig skin, showed that peel adhesion force was not compromised by the presence of glycerol up to 50 phr when compared to a pristine silicone sample. However, glycerol-silicone adhesives with 60 and 70 phr of glycerol exhibited some instances of cohesive failure. Tack tests produced similar results: tack force was not compromised by the presence of glycerol up to 50 phr—establishing this value as the maximum amount of glycerol it was possible to incorporate into the silicone adhesives without compromising performance. Overall, increased fluid handling properties were intended to improve adhesive performance over time, avoiding undesired failure caused by excessive liquid secretion from the wound and/or skin (e.g., sweat and/or wound exudates). Perspiration simulation experiments were therefore performed in order to demonstrate that the glycerol-silicone adhesives could perform adequately in the presence of consistent amount of liquids secreted from the skin. An artificial skin membrane with a porous structure was used as the substrate, and the perspiration simulator had the ability to “sweat” at constant pressure. Adhesives’ peel force was recorded before and after sweating. These simulations showed no remarkable variations in peel force between dry and wet adhesives, and almost no failures—thereby demonstrating glycerol-silicone adhesives’ enhanced fluid handling properties.

The second part of the project investigated the possibility of incorporating an active compound into glycerol-silicone adhesives, with the ultimate goal of conferring antimicrobial properties capable of preventing bacterial infections in chronic wounds. The compound chosen for these studies was an antiseptic drug called octendine (Oct), whose chemical structure is comprised of
two amino groups. Oct’s incorporation into glycerol-silicone adhesives proved challenging due to inhibition of the hydrosilylation reaction, so a new strategy was developed to cure glycerol-silicone adhesive through hydrosilylation in the presence of octenidine. Successful curing was achieved by the formation of inclusion complexes with cyclodextrins (CDs). CDs:Oct molar ratios ranging from 0.25 to 4 were tested, and rheological characterization showed that complexes with a HPβCD:Oct ratio > 1 allow the incorporation of 1 wt.% Oct without compromising the adhesive’s mechanical properties. This finding demonstrated that CDs suppress Oct’s inhibition of hydrosilylation. The interaction between HPβCD and Oct through the formation of inclusion complexes was further characterized and confirmed using 2D ROESY spectroscopy. Finally, the possibility of releasing Oct from glycerol-silicone adhesives in order to generate antimicrobial activity was also demonstrated. Glycerol-silicone adhesives with 50 phr of glycerol, 1 wt.% of Oct, and a HPβCD:Oct molar ratio of 2 showed higher antimicrobial activities against *P. Aeruginosa* and *E. Coli* than Coloplast commercial samples containing silver, Mepitel Ag. Both release rate and antimicrobial properties were found to depend on glycerol content; in other words, a minimum release rate was required in order to kill the bacteria.

Overall, the favorable properties obtained in the glycerol-silicone adhesives generated here, as well as their relatively simple preparation, indicate the successful development of a new adhesive formulation with improved fluid handling and new antimicrobial properties. Glycerol-silicone adhesives display significant potential candidates for advanced wound care applications which require effective healing of chronic wounds as well as prevention of bacterial infections.

### 6.2 Outlook

The glycerol-silicone adhesives developed in this project demonstrated increased water absorption and permeability, properties which, combined with the release of active substances, show promise for applications in the healthcare/medical industries.

It would be interesting to find and test other types of silicone adhesive kits than the MG7-9900 used in this thesis. I had begun to preliminarily mix different silicone adhesive kits with glycerol before the COVID-19 emergency, but was unfortunately unable to investigate them thoroughly. Due to the industrial nature of this thesis, I cannot go into detail about what new silicones (e.g. producing companies, brands) I used. However, I can state that I found at least two types of silicone that allowed the incorporation of more than 100 phr of glycerol without compromising the integrity of the adhesive network. In addition, preliminary peel tests revealed that peel forces were not compromised by such high glycerol concentrations. Incorporating larger amounts of glycerol into silicone adhesives would enhance water absorption and permeability even further than in the system investigated here, and would also increase the glycerol content-dependent release rate of octenidine. This means that, in principle, it would be possible to incorporate a relatively minor amount of octenidine into the system while still ensuring an effective dosage for killing bacteria. In general, the use of smaller effective doses is always desirable in pharmaceutical/medical applications. Finally, tuning the release rate to the glycerol content opens up the possibility of designing targeted therapies with controlled drug delivery.
It would be also interesting to investigate the incorporation of drugs other than octenidine into glycerol-silicone adhesives. The release kinetics of different molecules should therefore be tested. Different types of cyclodextrins could also be investigated; in particular, it would be worth studying whether other types of cyclodextrins can even more effectively suppress the interference of platinum-inhibiting molecules with hydrosilylation curing. In terms of release studies, it would be worthwhile to compare drugs complexed with cyclodextrins to those released in their free form.

The bacteria used for the antimicrobial tests performed in this thesis were prepared in a 0.9 wt.% NaCl solution. To simulate more realistic conditions, it would be beneficial to test antimicrobial activity in other types of media, such as some sort of simulated wound fluid, or possibly even blood.

The perspiration simulations performed here indicated that glycerol-silicone adhesives maintain their adhesive properties in the presence of large amounts of liquid. However, these results should be compared in future with actual clinical studies in which glycerol-silicone adhesives are tested on humans under similar conditions.

Finally, given the industrial nature of this project, it would be interesting to scale up the manufacturing process of glycerol-silicone adhesives to a pilot/production level in order to investigate whether increased production results in any compromise of the expected adhesive requirements.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>βCD</td>
<td>Beta-cyclodextrin</td>
</tr>
<tr>
<td>CDs</td>
<td>Cyclodextrins</td>
</tr>
<tr>
<td>CFU</td>
<td>Colony forming units</td>
</tr>
<tr>
<td>D</td>
<td>Drug molecule</td>
</tr>
<tr>
<td>DFUs</td>
<td>Diabetic foot ulcers</td>
</tr>
<tr>
<td>E. Coli</td>
<td>Escherichia coli</td>
</tr>
<tr>
<td>ECM</td>
<td>Extracellular matrix</td>
</tr>
<tr>
<td>FEP</td>
<td>Fluorinated ethylene propylene</td>
</tr>
<tr>
<td>HPβCD</td>
<td>(2-hydroxypropyl)-beta-cyclodextrin</td>
</tr>
<tr>
<td>LVE</td>
<td>Linear viscoelastic</td>
</tr>
<tr>
<td>MQ</td>
<td>Methyl silicone</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOE</td>
<td>Nuclear Overhauser effect</td>
</tr>
<tr>
<td>Oct</td>
<td>Octenidine</td>
</tr>
<tr>
<td>P. Aeruginosa</td>
<td>Pseudomonas Aeruginosa</td>
</tr>
<tr>
<td>PDMS</td>
<td>Polydimethylsiloxane</td>
</tr>
<tr>
<td>Phr</td>
<td>Glycerol weight amount per hundred parts of silicone</td>
</tr>
<tr>
<td>PSA</td>
<td>Pressure sensitive adhesive</td>
</tr>
<tr>
<td>Pt</td>
<td>Platinum</td>
</tr>
<tr>
<td>PU</td>
<td>Polyurethane</td>
</tr>
<tr>
<td>PUs</td>
<td>Pressure ulcers</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>RH</td>
<td>Relative humidity</td>
</tr>
<tr>
<td>ROESY</td>
<td>Rotating frame Overhauser effect spectroscopy</td>
</tr>
<tr>
<td>SI</td>
<td>Supplementary information</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>UV-vis</td>
<td>Ultraviolet-visible spectroscopy</td>
</tr>
<tr>
<td>VLUs</td>
<td>Venous leg ulcers</td>
</tr>
<tr>
<td>WVTR</td>
<td>Water vapor transmission rate</td>
</tr>
</tbody>
</table>
Bibliography


(8) Busse, B. Wound Management in Urgent Care; Springer Berlin Heidelberg: Folsom (CA) USA, 2016. https://doi.org/10.1007/978-3-319-27428-7.


<table>
<thead>
<tr>
<th>Reference</th>
<th>Author(s)</th>
<th>Title</th>
<th>Journal</th>
<th>Year</th>
<th>Volume</th>
<th>Issue</th>
<th>Pages</th>
<th>DOI</th>
</tr>
</thead>
</table>


62


(84) Liu, L.; Kuffel, K.; Scott, D. K.; Constantinescu, G.; Chung, H. J.; Rieger, J. Silicone-


(112) Renvoise, J.; Burlot, D.; Marin, G.; Derail, C. Adherence Performances of Pressure Sensitive Adhesives on a Model Viscoelastic Synthetic Film: A Tool for the


Appendix A

The following appendix is the final accepted version of the article “Glycerol-silicone adhesives with excellent fluid handling and mechanical properties for advanced wound care applications”. It was available online June 17th 2020 and in print June 2020.

The article is available online here: https://doi.org/10.1016/j.ijadhadh.2020.102667 and the citation of the article is given below.


Contributions: Johannes Eiler, PhD Student at DTU Chemistry and Coloplast A/S – Adhesives, is the inventor of the sweat model. All remaining work in this chapter, including analysis of the experimental data, was performed by Valeria Chiaula, with supervision from Piotr Mazurek, Anders Christian Nielsen and Anne Ladegaard Skov.
Glycerol-silicone adhesives with excellent fluid handling and mechanical properties for advanced wound care applications

V. Chiaula, P. Mazurek, J. Eiler, A.C. Nielsen, A.L. Skov

PII: S0143-7496(20)30130-5
DOI: https://doi.org/10.1016/j.ijadhadh.2020.102667
Reference: JAAD 102667

To appear in: International Journal of Adhesion and Adhesives

Received Date: 15 December 2019
Accepted Date: 30 May 2020


This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 Published by Elsevier Ltd.
Glycerol-silicone adhesives with excellent fluid handling and mechanical properties for advanced wound care applications

V. Chiaula\textsuperscript{a, b}, P. Mazurek\textsuperscript{b}, J. Eiler\textsuperscript{b, c}, A. C. Nielsen\textsuperscript{b}, A. L. Skov\textsuperscript{a*}

\textsuperscript{a} Danish Polymer Centre, Department of Chemical and Biochemical Engineering, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark.

\textsuperscript{b} GRD Technology – Adhesives, Coloplast A/S, DK-3050 Humlebæk, Denmark.

\textsuperscript{c} Department of Chemistry, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark.

Keywords: glycerol, silicone, wound care, fluid handling, absorption

* Corresponding author: al@kt.dtu.dk

Abstract

Adhesives with improved fluid handling and stable mechanical properties are gaining increasing interest in wound care due to improved wound healing conditions. Silicone adhesives possess in general excellent oxygen permeability but poor liquid water absorption and transport due to their inherent hydrophobicity. Herein, we present a novel glycerol-silicone hybrid adhesive with improved fluid handling properties as a result of the incorporation of relatively monodisperse glycerol droplets distributed homogenously throughout the silicone adhesive. The discrete glycerol droplets promote water absorption when the adhesive comes into contact with an aqueous phase due to the hygroscopic nature of glycerol. Additionally, the adhesives’ performance, evaluated in terms of mechanical properties, peel, and tack, is shown not to be compromised by presence of the glycerol droplets, mainly due to the so-called solid stiffening effect introduced by their interfacial energies.

1. Introduction

Increased numbers of patients are affected by wounds and, in particular, chronic wounds [1,2], as a consequence of diabetes and other chronic diseases that may affect wound healing [3]. To avoid chronic wounds and to promote faster healing, it is important to maintain a humid environment in the wound
while at the same time ensure that the surrounding skin is not macerated due to presence of too much liquid (water, sweat, and exudate) in close contact with the wound [4,5]. Currently, many adhesives are far too impermeable to avoid maceration over long periods, and therefore, as an example, holes are implemented into the adhesives to allow for moisture transport via larger microscopic or even macroscopic channels. However, these only help locally and maceration may still occur away from the holes. Also, the implemented holes may collapse over time and deplete. A more dense and homogeneous distribution of highly water conducting channels is therefore required for ideal wound healing.

Pressure sensitive adhesives (PSAs) constitute a widely used class of adhesive material in consumer products [6,7]. For wound care applications, the PSAs must be soft and viscoelastic, yet solid, to adapt to human skin in a comfortable manner [8]. Silicone adhesives are usually off-stoichiometric silicone elastomers that remain close to their gelation threshold (i.e. with a low cross-linking degree) [9,10], and within the field of advanced wound care, silicones are currently the preferred adhesive system due to their gentle skin adhesion properties [11–13]. Their softness and low surface tension facilitate polymer chain mobility on and into the skin, thereby creating a large, intimate contact area on the uneven skin surface [14]. In addition, silicone adhesives do not leave a significant residue on the skin when removed, and therefore they are considered atraumatic [15].

To avoid maceration, a wound care adhesive should allow for effective moisture transmission at the skin-adhesive interface. Due to large mobility of the silicone polymer chains (silicone has a high free volume at room temperature), silicone adhesives have excellent oxygen permeability and a high water vapor transmission rate (WVTR) [8,16], and therefore handle transport of gaseous substances well. However, due to their inherent hydrophobic nature, current silicone adhesive solutions are challenged when it comes to fluid handling, in that basic perspiration from the patient’s skin can cause the dressing to lose its adhesive properties and eventually fall off. Failure occurs if the amount of sweat produced by the patient’s skin is greater than the sum of absorption capacity and the permeability of the adhesive [17–21].

To overcome the hydrophobicity of the silicone surface, grafting of hydrophilic moieties to the silicone surface has been investigated [22–24]. The resulting increase in water transport is initially large but over time the silicone depletes the hydrophilic surface due to the low surface energy of the hydrophobic silicone by absorbing the hydrophilic groups into the bulk of silicone [25].
Two-phase glycerol-silicone hybrid elastomers which, depending on formulation, possess a bi-continuous or closed cell structure have been thoroughly described by Mazurek et al [26]. They can be shaped as thin films, bulk elements and foams [27]. Both constituents furthermore are known to be biocompatible and non-toxic [28–30]. The glycerol-silicone composites are created in a simple manner by providing high shear forces to mixtures of glycerol and silicone prepolymers [26]. In this way, physically stable glycerol-in-silicone emulsions are formed which, upon cross-linking of the silicone phase, form free-standing two-phase elastomers. As reported previously, upon contact with an aqueous phase, the composites absorb significant amounts of water [26,31,32].

The use of glycerol-silicone composites as skin adhesives has not been described before. Herein, we present a novel glycerol-silicone hybrid adhesive with improved fluid handling properties as a result of micrometer-sized glycerol droplets dispersed evenly throughout the silicone adhesive. We find that incorporating glycerol increases the water absorption and permeability of silicone adhesives, thereby making them potential candidates for use as wound care adhesives.

2. Experimental

2.1 Materials

A commercially available two-part system (part A and part B) hydrosilylation-curing MG7-9900 soft silicone adhesive kit was purchased from DowDuPont Inc.™. Glycerol was kindly provided by Emmelev A/S, Denmark. Perylene (synthesis grade) and sulforhodamine B acid chloride (technical grade) were acquired from Sigma-Aldrich, Denmark. All the components were used as received. Polyethylene terephthalate (PET) and polyurethane (PU) backing films were provided by Mitsubishi Polyester Film (Germany) and by Coveris (UK), respectively. A fluorinated ethylene propylene (FEP) release liner was purchased from Lohmann (UK). A UV-curable negative photoresist polymer film (MX5050) used to create the artificial skin was provided by Dupont (USA).

2.2 Methods
2.2.1 Sample preparation

The two components of the commercial soft silicone adhesive kit were mixed in a 1:1 ratio by weight, as recommended by the manufacturer. Subsequently the desired amount of glycerol was added to the silicone adhesive premix. The abbreviation ‘phr’, used to describe glycerol content in all compositions, corresponds to glycerol weight per hundred parts of silicone adhesive. So, for example, 10 phr means that 10 g of glycerol was used per 100 g of the silicone adhesive premix. Samples name were formed using the GX pattern, where ‘G’ and ‘X’ stand for glycerol and glycerol phr added to silicone adhesive premix, respectively (for instance, G40 is 40 phr of glycerol). The mixtures were stirred for 2 min in two steps: 1 min by hand-mixing with a spatula and 1 min at 3500 rpm with a dual asymmetric centrifuge SpeedMixer DAC 150 FVZ-K (Germany). No additional degassing of the formulations was necessary. The obtained glycerol-in-silicone emulsions were coated at 23 mm/s onto a PET or PU backing film with commercial knives (with gap sizes of 0.4 mm or 0.8 mm) and an RK K Control Coater to obtain adhesives with thicknesses around 0.3 or 0.6 mm. The samples were subsequently cured at 80 ± 1°C for 1 h and then cut in a pre-defined shape. All samples were covered with an FEP release liner after coating, and before any measurement took place, this liner was removed. Adhesive thicknesses were then measured using a digital thickness gauge (Mitutoyo, Germany).

2.2.2 Morphology of glycerol-silicone adhesive and determination of glycerol surface area per volume of adhesive

A Leica DM LB optical microscope was used to investigate the morphologies of the uncured samples, whilst a confocal Leica TCS SP5 X was used to analyse the morphology of cured composites. In order to demonstrate the distribution of glycerol droplets into silicone, we labelled each phase with different colour dyes. Sulforhodamine B and perylene were used to dye the glycerol and the silicone phases, respectively. To determine the glycerol surface area per volume of adhesive, glycerol spherical droplets in the formulation were measured in terms of their diameter by counting the droplets directly from microscopy pictures, using ImageJ software. The detailed calculations are reported in Supplementary Information (SI).

2.2.3 Fluid handling capability of adhesives

To measure the permeability of the adhesives, specimens of area (A) 10 cm² and thickness 0.3 mm were cut out and placed into Paddington chambers, which are the commonly used set-up for measurements of fluid handling capacity and permeability according to the European Standard EN 13726-1 2002. Each
chamber was closed with a lid when the experiments started. The test chambers with fixed samples and lids were weighed ($W_1$). Subsequently, 20 mL of saline test solution (8.298 g NaCl and 0.368 g CaCl$_2$·(H$_2$O)$_2$ in 1 L of deionized water) was transferred to each chamber and the weights recorded ($W_2$).

The assembled test chambers were closed and placed on a plastic tray inside a climatic test cabinet at 37 ± 1 °C and 15% RH. The water was in direct contact with the adhesives. After 24 h, the test chambers were removed from the climatic cabinet and left at room temperature for 30 min. After this time, the test chambers were weighed again ($W_3$). Five repetitions of the test were done for each compositions. Permeability, or WVTR, over 24 h was reported as:

$$WVTR \times \Delta t = \frac{(W_2-W_3)}{A} \quad (1)$$

To determine the water absorption capability of the adhesives, specimens of area (A) 10 cm$^2$ and thickness 0.3 mm were weighed ($W_0$) and subsequently immersed in saline test solution for 24 h. After 24h, samples were thoroughly dried with absorbing paper to remove any residual water droplets from the surface and weighed again ($W_{24}$). Three repetitions of the test were run for each composition. The water absorption over 24 h was reported as:

$$WA \times \Delta t = \frac{(W_{24}-W_0)}{A} \quad (2)$$

2.2.4 Linear viscoelastic measurements

Linear viscoelastic (LVE) properties of glycerol-silicone adhesives were measured with a Discovery HR-2 Hybrid Rheometer (TA Instruments) using a parallel-plate geometry 20 mm in diameter. The instrument was set to a controlled strain mode ensured to be within the linear regime. Strain was set at 1%, and frequency sweeps were performed from 100 Hz to 0.01 Hz at 32 °C. Samples thicknesses were 0.6 mm. Measurements were done in triplicate for each composition.

2.2.5 Peel tests on stainless steel plates and pig skin

Samples with a thickness of 0.3 mm were cut in 25 mm x 100 mm rectangles. A TESA 4651 auxiliary tape was then cut in 25 mm wide strips, which in turn were glued to the adhesives. Each adhesive was carefully applied manually to a steel plate and/or pig skin. An automatic roll-down laminating machine (applied pressure 2 kg and rolling speed 300 mm/min) designed for the purpose was used to minimize air inclusion between sample and substrate. Steel plates and/or pig skin with mounted adhesives were then equilibrated for 30 min in a test cabinet at 32 ± 1 °C. Subsequently, peel tests were performed using a Texture Analyser (TA) XT Plus (Micro Systems Ltd., UK). Peel rate and peel angle were set at 5
mm/s and 180°, respectively, for the adhesives mounted on steel plates. For the tests performed on pig skin, peel rate was 5, 1 and 0.1 mm/s, respectively. The peel angle was kept constant at 180°. Five measurements for each composition were performed and results were averaged.

2.2.6 Perspiration simulator and perspiration experiments

The simulator consisted of an artificial skin membrane, mimicking human skin in terms of topography, water contact angle, and sweat pore distribution, was glued to a sweat reservoir. A sweat pore density of 100 cm⁻² was chosen to represent skin in the abdominal area [33]. Dimensions of artificial skin were 25 mm x 40 mm. Adhesives for the experiments were cut to the same dimensions and then applied to the artificial skin with a defined pressure and over a set time. The reservoir was connected to a custom-made device for controlling the desired height of the water column and thus the desired pressure during the test. The tank was filled with a saline solution of 0.154 M NaCl. The height of the tank was set to achieve a pressure of around 2 kPa, which corresponds to typical pressures observed during perspiration [34]. The tank was connected to the inlet of the reservoir through a tube and the sweat flow was controlled through a valve connected to a flow sensor (Elveflow, France). After 30 min, the sweat flow was stopped and adhesives were peeled off the artificial skin to determine the effect of perspiration on peel force. Peel tests were performed using an Instron 5943. Peel angle and peel rate were set at 90° and 5 mm/s. Three perspiration experiments followed by peel tests were run for each composition. As references, samples were contacted with the artificial skin for 30 min, with no exposure to saline composition, and subsequently peeled off.

2.2.7 Tack tests

A modified version of the Loop Tack method (AST D6195-03) was used for testing. The loop was made of a rectangular strip of printing-paper, dimensions were 25 mm x 175 mm and it was closed with a 25 mm x 25 mm square of double-sided tape. The loop was then mounted in a clamp-fixture on an Instron 5543 and placed with a 2-4 mm gap between the loop and the adhesive. Adhesives were cut to dimensions of 25 mm x 100 mm and mounted on top of a T-shaped platform fixed in the lower grip of the Instron 5543. The loop was lowered until it completely covered the adhesive at a rate of at 5 mm/s, followed by immediate reversal at the same rate, until complete detachment from the sample and return to the initial position. The maximum peak and tack forces were measured from the obtained force curve. Five measurements for each sample were performed and results were averaged.
3. Results and discussion

3.1 Morphology of glycerol-silicone adhesives and determination of glycerol surface area per volume of adhesive

Glycerol-silicone adhesives were produced by applying high shear forces to the glycerol and adhesive premixes. Silicone constitutes the continuous phase with dispersed, discrete droplets of glycerol homogeneously distributed within. Confocal microscopy images of cross-sections of cured adhesives with varying content of glycerol are shown in Fig. 1. Confocal image analysis of the resulting morphology shows that with increased loading of glycerol, the glycerol droplets become larger and more densely distributed despite identical mixing and curing conditions. This is in contrast to results for the previous studies of mixing glycerol into silicone elastomers, where the diameter of the droplet remained constant for a wide range of glycerol loadings undergoing the same mixing and curing procedures [26]. However, the previously investigated elastomers also possess a significant fraction of silica fillers that are believed to stabilize the initial emulsions and thereby also the resulting material. In the current study, the silicone adhesive formulations are filler-free, therefore the stabilizing effect is missing. Furthermore, when glycerol loading increases, more droplets are generated during the emulsion preparation and, additionally, the space between droplets decreases. Therefore, the possibility of droplets agglomeration increases, explaining the larger droplets observed for high-glycerol loading adhesives. The average droplet diameters as function of glycerol loading are shown in SI. To facilitate the understanding of the counterintuitive rheological behavior in the following sections, the surface area of the droplets per total volume of adhesive is required. Knowing the diameter of a glycerol sphere \( (D_i) \) and the glycerol volume fraction in a silicone adhesive \( (\varphi) \), the internal surface area \( (\sum N_i A_i) \) per volume of adhesive volume \( (V_{tot}) \) is calculated by means of simple geometry as:

\[
\frac{\sum N_i A_i}{V_{tot}} = \frac{\varphi \sum N_i A_i}{\sum N_i V_i} = \frac{6 \varphi \sum N_i D_i^2}{\sum N_i D_i^2} \quad (3)
\]

since the volume of glycerol can be written as \( \sum N_i V_i = \varphi V_{tot} \) and the diameter of glycerol spheres can be written as \( D_i = \sqrt[3]{\frac{6 V_i}{\pi}} \).

The estimated internal glycerol-silicone surface area per volume of adhesive was determined from averaging over 1,000 droplets. The achieved results are shown in Fig. 2. The internal surface area...
steadily increases until it reaches a maximum at 40 phr loading. Subsequently, the extra loading of glycerol no longer increases the internal surface area but rather results in significantly larger droplets - and thereby a reduction of the internal surface area despite the introduction of more glycerol.

![Confocal microscopy images of cured glycerol-silicone adhesives. Higher glycerol amount results in thinner spacing between droplets and in larger droplet diameters. 10, 40 and 70 phr correspond to volume fraction of 7%, 23% and 35%, respectively.](image1)

![Glycerol surface area per volume of adhesive determined from image analysis of confocal microscopy images.](image2)

**Fig.1.** Confocal microscopy images of cured glycerol-silicone adhesives. Higher glycerol amount results in thinner spacing between droplets and in larger droplet diameters. 10, 40 and 70 phr correspond to volume fraction of 7%, 23% and 35%, respectively.

**Fig.2.** Glycerol surface area per volume of adhesive determined from image analysis of confocal microscopy images.

### 3.2 Water absorption and permeability
For the glycerol-silicone adhesives, water absorption is an effect of building up osmotic pressure. As water moves down its osmotic potential gradient, it starts to fill the glycerol domains embedded in the silicone adhesive. It was previously shown that water absorption is more efficient both with respect to rate and total capacity at increasing glycerol loadings for glycerol-silicone elastomers, i.e. more densely cross-linked silicones than the adhesives [26]. It is also known that the softer the silicone, i.e. reduced cross-linking density, the more water can potentially be absorbed by the formulations, as lower elastic stress has to be overcome to expand the glycerol domains [35,36]. Results for water absorption and permeability over 24 h are presented in Fig. 3 and a sketch of the water absorption mechanism is illustrated in Fig. 4. The buildup of sweat at the skin-adhesive interface is unfavorable with respect to adhesion as well as it causes maceration. The glycerol-silicone elastomers allow for removal of the liquid at the interface due to the hygroscopic nature of glycerol. As expected, water absorption increased with increasing glycerol content. Specifically, water uptake increased up to 0.75 g/10 cm²/day for adhesives containing 50 phr of glycerol compared to the pristine silicone adhesive sample. However, it is surprising that the absorption of adhesives with 60 and 70 phr of glycerol did not increase further, but stabilized at similar level as the 50 phr adhesive. The reduced absorption level after 24 h observed for these samples can be explained by the determined glycerol surface areas per volume of adhesive, reported in Fig. 2. As a result of larger average droplet sizes in the higher-glycerol-loading formulations, the glycerol surface area per volume of adhesive did not increase further after 50 phr, but actually decreased for 60 and 70 phr adhesive samples. Hence, the available surface area of glycerol exposed to water during the water absorption experiments is smaller than the available surface area in 40 and 50 phr samples, thus explaining the lower absorption levels after 24 h. In other words, the interfacial area governs the rate of water uptake. Furthermore, since the 60 and 70 phr adhesives did not reach their final absorption capacity after 24 h, the recorded data is transient and this explains the deviation from the behavior of the silicone elastomers, where water uptake scales with loading of glycerol.

The permeability of glycerol-silicone adhesives increased in line with glycerol content as expected. Specifically, an increase of 230% for the 70 phr adhesive samples was observed compared to the pristine silicone sample. When glycerol is introduced in the adhesive formulation, the volume fraction of the silicone is reduced and therefore the molecules need to permeate through less. As the permeability is highly dependent on the thickness of the silicone layer, the thinner the glycerol loading, the thinner the actual silicone barrier that water vapour has to overcome.
In general, the overall enhancement of fluid handling capabilities of glycerol-silicone adhesives in a 24 hours period, facilitated by incorporating emulsified glycerol, was proved, with up to 50 times in water absorption and 3 times increase in permeability compared to the pristine silicone adhesive.

**Fig.3.** Water absorption and permeability of glycerol-silicone adhesives with different glycerol loadings measured at 37 °C and 15% RH over 24 h. A period of 24 hours is chosen as a representative time for a wound care adhesive. None of the glycerol-silicone adhesives has received their full absorption capacities in the given period due to the transient nature of the adhesives where they simultaneously transport water vapor through the material and water absorption in the glycerol.

**Fig.4.** Schematic illustration of the water absorption mechanism by glycerol droplets.
3.3 Linear viscoelastic properties of glycerol-silicone adhesives

Fig. 5A and 5B illustrate storage moduli ($G'$) and dissipation factors ($\tan \delta = G''/G'$) as a function of frequency for adhesives with glycerol loadings from 0 to 70 phr. Data shows that the adhesives soften in their linear viscoelastic response (i.e. lower $G'$) to increasing glycerol content, as expected, due to the larger volume fraction of liquid. However, counterintuitively, $\tan \delta$ decreases across the entire frequency range in line with increased loading of glycerol, thereby indicating that the elastic response compared to the viscous response increases as the samples contain more and more liquid. This can be explained by the elasticity of the cross-linked emulsions having two elastic components, namely the elasticity arising from silicone network and the internal interfacial energies, whereas glycerol does not contribute much to the viscous loss at the given temperature. The results thereby indicate that the interfacial energies constitute a major contribution to elasticity for the soft silicone adhesives.

Furthermore, from figure 5B it can be seen that with increased glycerol loading the characteristic relaxation time (as identified by $\tau = 1/\omega$ for the frequency for which $\frac{d(\tan \delta)}{d\omega} = 0$, where $\tau$ and $\omega$ are relaxation time and angular frequency, respectively) decreases. This indicates that - despite the less lossy nature of the adhesive with increased glycerol - the dynamics within the adhesive is speeded up at least a decade from 0 phr to 70 phr. This agrees well with higher mobility at the interfaces compared to the bulk properties.
3.4 Peel force analysis of glycerol-silicone hybrid adhesives on stainless steel plates

Peel forces of adhesives from stainless steel plates and their failure modes were investigated. The results are summarized in Fig. 6A. Initially, a sharp decrease in peel force for the G0 to G20 samples is observed, and then no significant variations in peel forces are detected for increased glycerol loadings up to 50 phr. To explain this behavior, first of all, the true thickness of adhesive layer in contact with the substrate must be considered. The thickness of the adhesive $d$ can be related to the peel force $F_{\text{peel}}$ via the following equation [10]:

$$
\frac{F_{\text{peel}}}{dW_G} = g(\tan \delta_{\omega_{\text{peel}}})
$$

(4)

where $W$ is the width of adhesive, $G_0$ is the zero-shear modulus and $\omega_{\text{peel}}$ is the frequency of the peeling experiment determined as:

$$
\omega_{\text{peel}} = \frac{V_{\text{peel}}}{d}
$$

(5)

where $V_{\text{peel}}$ is the peel rate of the peeling experiments. $g$ is a function, most commonly in the form of $g(x)=x$, and with this assumption the peel force per width of adhesive can be written:

$$
\frac{F_{\text{peel}}}{W} = dG_0 \tan \delta_{\omega_{\text{peel}}}
$$

(6)

The true thickness of the adhesive layer instantaneously reduces when glycerol is introduced into the adhesive. This is due to the presence of discrete glycerol droplets, since the thickness of the contacting adhesive is no longer the thickness of the film but rather a distance closely related to the average thickness between droplets. This can explain the rapid drop in peel force from 0 to 10 phr. At the same time, at the peel frequency of $(5 \text{ mm s}^{-1} / 0.30 \text{ mm} = 17 \text{ s}^{-1})$ there is not much change in $\tan \delta$ or $G_0$ between 0 and 10 phr. Upon further increases in glycerol loading, the peel force remains constant within experimental uncertainty, due to a combination of no significant reduction in $d$ and a small increase in $G_0$, caused by a stiffening effect from the increased number of droplets in the adhesive. Style et al [37,38] showed that surface tension acts to keep liquid inclusions spherical, thus opposing any applied stretch that would make liquid droplets elliptical.
All the compositions, from G0 to G50, exhibited adhesive failure at all frequencies. When glycerol loadings exceeded 50 phr, some instances of cohesive failure were observed, therefore the results were not included in the comparison. Cohesive failures at high loadings are addressed to the large fraction of liquid and thereby less adhesive to withhold the stresses and increased sensitivity to imperfections. As a result, the local stresses on some polymer strands become very high, and cause the adhesive to fail.

Fig. 6. A) Peel average forces of silicone adhesives with various glycerol loadings on stainless steel plates. Peel force decreased in samples containing glycerol. No significant variations in peel forces were observed from G20 to G50. All compositions from G0 to G50 exhibited adhesive failure mode. B) Peel force vs. loss tangent measured at the peel frequency. Peel force decreases with tan δ from G0 to G20 samples, but remains constant within experimental uncertainty from G20 to G50 samples.

From Fig. 6B it can also be seen that at low loadings the expected scaling of the peel force with tan δ prevails whereas for high loadings the scaling departs, probably due to the larger droplets and the resulting interplay between liquid stiffening and larger thickness of contact layer.

3.5 Peel force analysis of glycerol-silicone adhesives on pig skin

Peel forces of glycerol-silicone adhesives from pig skin were investigated at three different peel rates. The results are presented in Fig. 7 and show that the peel force decreases in line with the decreasing peel rate, indicating a correlation between mechanical response and peel velocity. This is in line with
prior studies on PSAs [39–43], that have shown that the relationship between peel force ($F$) and peel velocity ($v$) at the same peel angle can be described by:

$$\frac{F}{b} = kv^n$$  \hspace{1cm} (7)

Where $b$ is the width of the adhesive, $k$ is a constant that depends on the peel angle and the thickness of the PSA. $n$ is a constant related to the intrinsic properties of the PSA [39]. From Fig. 7 it is clear that – within experimental uncertainty – the peel forces of all the investigated adhesives, including the pristine silicone adhesive, behave identically with variation in peel rate. Therefore, it can be concluded that the intrinsic properties of silicone adhesives are maintained.

In addition, results show that overall there are no remarkable differences in peel forces from the G0 to G50 samples. This behavior is slightly in contrast to the peel forces from steel (Fig. 6), where a drop was observed from 0 to 10 phr reasoned to be due to introducing glycerol in the formulation, which reduces the true thickness of the adhesive layer in contact with the substrate. This deviation can be attributed to the competition between multiple factors. First, as discussed in the previous section, solid stiffening, as a result of glycerol inclusion, increases the experienced modulus. Secondly, as skin has an uneven surface compared to steel, the silicone chains can create a larger, intimate contact area with this substrate due to the high mobility of silicone chains at the interface.

All G0 to G50 compositions exhibited adhesive failure, and we observed instances of cohesion failure for adhesives containing 60 and 70 phr of glycerol. Therefore, these data were omitted.
3.6 Perspiration experiments and adhesives’ performance characterization

The adhesives’ performance under high-perspiration conditions was evaluated using the perspiration simulator ideated by Eiler et al [44,45]. This simulator recreates perspiration conditions similar to those occurring on human skin. Sweat glands typically exert pressure of approximately 2 kPa to generate perspiration rates up to 2 µL/cm²/min [33]. A simplified illustration of the simulator is shown in Fig. 8A. From Fig. 8B it can be seen that variations in peel forces between dry and wet samples were not remarkable. None of the compositions fell off the artificial skin during the experiments, with the single exception of G70. This suggests that almost all adhesives resist ≈ 2 kPa water pressure consistently. Moreover, glycerol-containing adhesives seem less affected (change from dry to sweat) by the simulated sweat pressure than G0. As discussed previously, as a consequence of fluid build-up in the interface skin-adhesive, adhesion failure may occur if the amount of liquid exceeds the absorbing capacity of an adhesive. Glycerol-silicone adhesives showed remarkable resistance during the sweat tests almost momentarily, indicating that glycerol may help remove eventual liquid-build-up at the adhesive-substrate interface, thus maintaining the adhesion level of dry adhesives as result of enhanced permeability.
Fig. 8. A) Schematic illustration of the perspiration’ experiments’ set-up. The height of the tank containing simulated sweat was set to obtain a pressure of \( \approx 2 \) kPa, resulting in a sweat rate of \( \approx 2 \) µL/cm\(^2\)/min. Sweat time was set at 30 min. The adhesive was in contact with the artificial skin, which was glued to the sweat reservoir. B) Peel average forces of silicone adhesives with various glycerol amounts on artificial skin. Adhesives were pulled at an angle of 90° and a speed of 5 mm/s. Data revealed no loss of adhesive properties in wet samples compared to dry samples.

3.7 Tack force analysis of glycerol-silicone hybrid adhesives

The tackiness of glycerol-silicone hybrid adhesives was investigated. An illustration of the tack test set-up is shown in Fig. 9A, and the results are shown in Fig. 9B. No significant variations in tack forces were observed when increasing glycerol content in the silicone adhesives. Similarly to the peel force, we believe that the tack force is also affected by the solid stiffening effect. Furthermore, the paper used for the test consisted of high porosity between paper fibers such that the more mobile silicone chains can establish an immediate, large intimate contact area with the paper, as hypothesized in the case of the pig skin (vide supra). When glycerol loadings exceeded 50 phr, some instances of adhesive failure were observed, therefore data were omitted.
4. Conclusions

A novel glycerol-silicone adhesive was successfully prepared from speed-mixing mixtures of silicone adhesives and glycerol into stable emulsions. Upon cross-linking of the continuous silicone phase in the emulsions, glycerol-silicone adhesives were obtained, with glycerol embedded in the polymer in the form of discrete droplets. The fluid handling properties of glycerol-silicone adhesives were significantly increased by incorporating glycerol, and peel adhesion tests on stainless steel plates and pig skin revealed that the adhesives’ performance was not compromised by incorporating glycerol up to 50 phr. Above 50 phr of glycerol (corresponding to volume fractions of 28%) some instances of cohesive failure were observed. Additionally, perspiration simulation experiments revealed that glycerol-silicone adhesives showed remarkable resistance under harsh conditions. This indicates that glycerol helps removing eventual liquid build-up at the adhesive-substrate interface as a result of enhanced permeability (up to 3 times increased compared to pristine adhesives) and water absorption (up to 50 times compared to pristine adhesives). Lastly, the tackiness was not compromised by adding glycerol to adhesives at a loading up to 50 phr.
The very favorable properties of the prepared adhesives as well as the simplicity of the preparation scheme indicate a simple adhesive with properties partly governed by the used silicone adhesive system as well as the loading of glycerol into it.

References


Glycerol-silicone adhesives with excellent fluid handling and mechanical properties for advanced wound care applications

V. Chiaula\textsuperscript{a, b}, P. Mazurek\textsuperscript{a}, J. Eiler\textsuperscript{b, c}, A. C. Nielsen\textsuperscript{b}, A. L. Skov\textsuperscript{a*}

\textsuperscript{a} Danish Polymer Centre, Department of Chemical and Biochemical Engineering, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark.

\textsuperscript{b} GRD Technology – Adhesives, Coloplast A/S, DK-3050 Humlebæk, Denmark.

\textsuperscript{c} Department of Chemistry, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark.

Keywords: glycerol, silicone, wound care, fluid handling, absorption

* Corresponding author: al@kt.dtu.dk

1. Morphology of cured glycerol-silicone adhesives and size distribution of glycerol droplets in the adhesives

The droplet size distribution of the cured glycerol-silicone adhesives was investigated as a function of glycerol loading. The average droplet size was evaluated by measuring the diameters of at least 100 neighboring droplets in each adhesive. Diameters were measured by marking of the droplets directly from microscopy pictures, using ImageJ software. Glycerol volume fractions in the investigated adhesives are calculated from Eq. (S3) are reported in Table S1. Confocal microscopy images of cross-sections of cured adhesives with varying content of glycerol are shown in Figure S1. Confocal image analysis of the resulting morphology shows that with increased loading of glycerol, the glycerol droplets become larger and more densely distributed despite identical mixing and curing conditions. However, the viscosity of the mixtures increases with increased glycerol loading. The droplet size distributions are presented in Figure S2. As illustrated, the average diameter increases in line with increasing glycerol loading.
Table S1. Conversion of phr into volume fractions.

<table>
<thead>
<tr>
<th>Sample name</th>
<th>Glycerol 'phr'</th>
<th>Glycerol volume fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>G10</td>
<td>10</td>
<td>7%</td>
</tr>
<tr>
<td>G20</td>
<td>20</td>
<td>13%</td>
</tr>
<tr>
<td>G30</td>
<td>30</td>
<td>19%</td>
</tr>
<tr>
<td>G40</td>
<td>40</td>
<td>23%</td>
</tr>
<tr>
<td>G50</td>
<td>50</td>
<td>28%</td>
</tr>
<tr>
<td>G60</td>
<td>60</td>
<td>31%</td>
</tr>
<tr>
<td>G70</td>
<td>70</td>
<td>35%</td>
</tr>
</tbody>
</table>

Figure S1. Confocal microscopy picture of all cured glycerol-silicone adhesives. The higher the amount of glycerol, the thinner the spacing between droplets, and the larger the droplets.
Figure S2. Average droplet diameters in glycerol-silicone adhesives with increasing glycerol loading. Diameters were determined by counting 100 droplets directly from microscopy pictures, using ImageJ software.

2. Determination of glycerol surface area per volume of adhesive

The spherical droplets of glycerol in the adhesive formulation were counted, and each diameter was measured and recorded. Simple geometric formulas for volume and surface area of a sphere were used:

\[ V_i = \frac{4}{3}\pi R_i^3 = \frac{1}{6}\pi D_i^3 \quad (S1) \]

\[ A_i = 4\pi R_i^2 = \pi D_i^2 \quad (S2) \]

where \( R \) and \( D \) are the radius and the diameter of a glycerol sphere, respectively, and \( i \) indicates an individual droplet, and 100 droplets were measured.

The glycerol volume fraction \( \varphi \) in formulation can be calculated by:

\[ \varphi = \frac{\text{phr}_G \rho_G}{\text{phr}_{NG} \cdot 100} \frac{\rho_G}{\rho_S} \quad (S3) \]
where phr\(_G\) is parts glycerol per hundred (100) of adhesive, \(\rho_G\) is the density of glycerol (\(\rho_G = 1.26 \text{ g/cm}^3\)) and \(\rho_S\) is the density of the silicone adhesive premix (\(\rho_S = 0.96 \text{ g/cm}^3\)).

The total volume of spheres of the \(N\) spheres can be written as:

\[
\sum_{i=1}^{N} V_i = \varphi V_{tot}
\]  \hspace{1cm} (S4)

Where \(V_{tot}\) indicates the volume of adhesive containing 100 glycerol droplets. Thereby, the surface area of the glycerol droplets in a given volume of material can be written as:

\[
\frac{\sum_{i=1}^{N} A_i}{V_{tot}} = \frac{\varphi \sum_{i=1}^{N} A_i}{\sum_{i=1}^{N} V_i} = \frac{6\varphi \sum_{i=1}^{N} D_i^2}{\sum_{i=1}^{N} D_i^3}
\]  \hspace{1cm} (S5)

3. Perspiration experiments and adhesives’ performance characterization

The flow rates for each tested sample are presented in Figure S3 (A-H). The experiment is conducted with a constant water pressure. The first part of the curve corresponds to filling up the setup and then the experiments runs at constant flow rate unless the adhesive fails at some of the pores. A failure is seen as an abrupt increase in flow rate followed by a buildup of liquid in the resulting failure cavity.
Appendix B

This appendix is the final draft of the manuscript for the article “Incorporation of a Hydrophobic and Platinum-Inhibiting Molecule via Cyclodextrins into Glycerol-Silicone Adhesives”. It is the final draft submitted to the Journal “ACS Applied Materials & Interfaces”.

Contributions: Peter Jeppe Madsen, Senior Researcher at DTU Chemical Engineering, helped with carrying the NMR studies in the lab. Lotte Stoklund Jensen, Team Manager and Scientist at Coloplast A/S, helped with carrying the antimicrobial tests. All remaining work in this chapter, including analysis of the experimental data, was performed by Valeria Chiaula, with supervision from Piotr Mazurek, Anders Christian Nielsen and Anne Ladegaard Skov.
Novel Antimicrobial Glycerol-Silicone Adhesives Releasing Octenidine

Incorporated via Cyclodextrins

V. Chiaula\textsuperscript{a, b}, J. Madsen\textsuperscript{a}, P. Mazurek\textsuperscript{a}, A. C. Nielsen\textsuperscript{b}, A. L. Skov\textsuperscript{a*}

\textsuperscript{a} Danish Polymer Centre, Department of Chemical and Biochemical Engineering, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark.

\textsuperscript{b} GRD Technology – Adhesives, Coloplast A/S, DK-3050 Humlebæk, Denmark.

Keywords: hydrosilylation, platinum catalyst, cyclodextrins, glycerol, silicone, adhesives, release

* Corresponding author: al@kt.dtu.dk

Abstract

Antimicrobial hydrosilylation cured silicone adhesives are sought after for advanced wound care applications. Octenidine is a promising drug, as it has a broad antimicrobial efficacy and no known bacterial resistance. However, its direct incorporation into silicone adhesives is challenging due to the amine functionality, which characterizes its chemical structure. Here, a new method is described for integrating octenidine into a glycerol-silicone hybrid adhesive through efficient hydrosilylation curing in the presence of octenidine. In its pure form, octenidine complexes efficiently with the platinum catalyst, thereby inhibiting the targeted hydrosilylation reaction and hindering curing. This obstacle is overcome by screening octenidine with cyclodextrins in homogeneously dispersed glycerol droplets, suppressing Pt inhibition in the silicone phase. Curing efficiency is demonstrated using rheology, which shows that it is possible to incorporate 1 wt.% of octenidine into glycerol-silicone adhesives in the presence of (2-hydroxypropyl)-\(\beta\)-cyclodextrin without affecting the adhesives’ mechanical properties. The interaction between octenidine and (2-hydroxypropyl)-\(\beta\)-cyclodextrin through an inclusion complex is confirmed by ROESY spectroscopy. Despite this screening, octenidine is still released efficiently from the glycerol-silicone adhesives upon contact with water, and a resulting antimicrobial action is subsequently demonstrated. This new technology constitutes a simple and efficient method for preparing wound care adhesives which actively inhibit the growth of two bacteria strains.

1. Introduction

Chronic wounds such as those often found in elderly and diabetic patients result from anomalies in cellular and molecular wound repair mechanisms.\textsuperscript{1} Specially designed materials are required in order to promote
correct wound healing and closure in these patients, among which skin adhesives are of significant current research interest. Broadly, a skin adhesive must allow moisture transport to avoid skin maceration due to the presence of excess liquids (mainly sweat and exudate) while still maintaining a humid environment in the wound.\(^2\,^3\) In addition, the ability to reduce or prevent bacterial infections would be a valuable feature in skin adhesives for chronic wounds.

Our previous work thoroughly described a new glycerol-silicone hybrid adhesive with significantly improved fluid handling properties resulting from a hydrosilylation curing reaction.\(^4\) Hydrosilylation cured silicone elastomers are widely used in industry—e.g., as biomedical devices and medical skin adhesives.\(^5\)–\(^7\) In general, hydrosilylation curing is a reliable method for preparing elastomers, as the reaction between the hydride and vinyl groups proceeds with high conversion and limited side reactions.\(^8\)–\(^11\) Nevertheless, preventing the inhibition or poisoning of the platinum (Pt) catalyst used in the hydrosilylation curing reaction remains a challenge in certain cases. In general, all substances are potential inhibitors that complex Pt with an efficiency comparable to or higher than that of the vinyl groups, since hydrosilylation curing requires a labile Pt atom complexed to the vinyl group of the silicone.\(^8\) For example, sulfur-, phosphorus- and nitrogen-containing compounds are all inhibitors, as they form competitive, irreversible complexes with Pt, resulting in slowed or unsuccessful curing.\(^8,\!^{12}\)

The healthcare industry is particularly interested in silicone adhesives with topical antimicrobial properties. Among topical antimicrobials, silver has been known for decades to prevent microbial growth, and more recently has been incorporated directly into silicone dressings.\(^13\)–\(^15\) Nevertheless, if in close contact to skin for an extended time, silver might be absorbed and lead to argyria, a local or systemic deposition of this metal in the skin itself.\(^16\) Chlorhexidine and triclosan are other commonly used antimicrobials. However, their extensive use is associated with antibiotic resistance and collateral effects, such as severe rashes and breathing difficulties.\(^17,\!^{18}\) Alternative antimicrobial products are therefore needed.

Octenidine (Figure 1C) is a positively charged bis-pyridinamine with a broad spectrum of antibacterial (both towards gram positive and gram negative bacteria) and antifungal properties—as well as some antiviral ones—and is capable of inhibiting biofilm formation.\(^19,\!^{20}\) In addition, octenidine has high biocompatibility, no known bacterial resistance, and is currently used as a wound cleansing agent and topical antiseptic.\(^21,\!^{22}\) Because its chemical structure includes long alkyl chains and two amine groups, octenidine’s direct incorporation into silicone-based skin adhesives is not trivial, since the alkyl chains
render it amphiphilic and the amine groups inhibit the hydrosilylation reaction. A new strategy to allow octenidine incorporation into silicone adhesives is thus required.

The use of glycerol-silicone elastomers as drug delivery systems was thoroughly described by Mazurek et al., who successfully demonstrated that glycerol domains act as reservoirs for small, hydrophilic molecules. Cyclodextrins are well known to have the ability to increase the aqueous solubility and stability of drugs with poor water solubility via the formation of inclusion complexes. In addition, cyclodextrins are known to improve drugs’ chemical stability, and in some cases to improve their efficiency. Due to the chair conformation of the glucopyranose units, cyclodextrins attain the shape of a truncated cone (Figure 1B), resulting in a hydrophobic central cavity and a hydrophilic outer surface. This particular conformation allows cyclodextrins to host hydrophobic molecules inside their cavity, improving their aqueous solubility.

In this work, we describe a new method for incorporating octenidine into glycerol-silicone adhesives via cyclodextrins. Specifically, we demonstrate a method for efficiently curing glycerol-silicone hybrid adhesives through hydrosilylation in the presence of octenidine via the formation of inclusion complexes, as demonstrated by ROESY spectroscopy. We find that cyclodextrins suppress the interference of octenidine with the Pt catalyst. We further demonstrate these adhesives’ ability to release octenidine, enabling the preparation of silicone adhesives with antimicrobial properties.

Figure 1. A) Chemical structures of the hosts β-cyclodextrin and (2-hydroxypropyl)-β-cyclodextrin. B) The truncated cone shape of cyclodextrins. C) Chemical structure of the guest molecule octenidine.
2. **Experimental**

2.1 **Materials**

A commercially available, two-part system (part A and part B) hydrosilylation curing soft silicone adhesive kit was used (MG7-9900 DowDuPont Inc.™). Glycerol was provided by Emmelev A/S (DK). β-cyclodextrin (βCD), (2-hydroxypropyl)-β-cyclodextrin (HPβCD), perylene (synthesis grade) and sulforhodamine B acid chloride (technical grade) were acquired from Sigma-Aldrich (DK). Octenidine dihydrochloride (Oct) was purchased from Dishman Group (UK). *P. Aeruginosa* (ATCC 27853) and *E. Coli* (ATCC 53498) bacteria strains were purchased from Miclev (SE). Lecithin was purchased from VWR Chemicals (DK). Coloplast A/S (US) provided commercial products containing silver (Mepitel Ag). Polyethylene terephthalate (PET) and polyurethane (PU) backing films were purchased from Mitsubishi Polyester Film (DE) and Coveris (UK), respectively. A fluorinated ethylene propylene (FEP) release liner was purchased from Lohmann (UK). All components were used as received.

2.2 **Methods**

2.2.1 **Sample preparation**

The two parts of the commercial soft silicone adhesive kit were weighed off in a 1:1 ratio, according to the manufacturer’s instructions. The desired amount of glycerol was subsequently added to the silicone adhesive premix. The abbreviation ‘phr’, used to describe glycerol content in all compositions, corresponds to glycerol weight per hundred parts of silicone adhesive: e.g., 20 phr means that 20 g of glycerol was used per 100 g of silicone adhesive premix.

For samples containing cyclodextrins (CDs) and octenidine (Oct), the mass of Oct was set at 1 wt.% of the combined mass of adhesive premix and glycerol in all experiments. This ratio was suggested by Coloplast A/S, with the goal of having a moderate amount of Oct in the final product. The amount of CDs was adjusted according to the desired CDs:Oct molar ratio; mixtures were prepared in molar ratios ranging
from 0.25 to 4, and dissolved in glycerol at 80 °C using magnetic stirring until clear solutions were obtained. The molar ratio \( r \) is defined as:

\[
\frac{n(CD)}{n(Oct)}
\]  

(1)

The desired amount of glycerol containing CDs:Oct mixture was subsequently added to the silicone adhesive premix. Sample names were formed using the patterns GX_Y, where ‘G’ and ‘X’ stand for glycerol and glycerol phr, respectively. ‘Y’ accounts for various parameters discussed in the following sections. Occasionally, ‘Y’ will be followed by a number, which stands for the molar ratio between CDs and Oct. A full description of all investigated samples can be found in Table 1 in the Supplementary Information.

The mixtures (silicone and glycerol, or silicone and glycerol containing CDs:Oct) were stirred for a total of 2 min: 1 min by hand-mixing with a spatula, followed by 1 min at 3500 rpm with a dual asymmetric centrifuge SpeedMixer DAC 150 FVZ-K (DE). No additional degassing of the formulations was necessary. The obtained glycerol-in-silicone emulsions were coated onto a PET backing film with a commercial knife (gap size of 0.4 mm) and a RK K Control Coater with a speed of 23 mm/s to obtain adhesives approximately 0.3 mm thick. The samples were subsequently cured at 80 ± 1°C for 1 h. All samples were covered with an FEP release liner after coating; this liner was removed before any measurement took place. Adhesive thicknesses were measured prior testing between the two liners using a Mitutoyo digital thickness gauge (DE).

### 2.2.2 Curing profiles of glycerol-silicone adhesives and linear viscoelastic measurements

Curing profiles of glycerol-silicone adhesives containing different CDs:Oct molar ratios were obtained by time sweep tests at 80 °C for 10 min on a controlled stress-strain ARES G2 rheometer (TA Instruments), using a parallel plate geometry 25 mm in diameter. The instrument was set to a controlled strain mode ensured to be within the linear regime. Frequency and strain were set at 1 Hz and 2 %, respectively. The gap between the plates was set to approximately 1 mm. Frequency sweeps were subsequently performed on the cured adhesives from 100 to 0.1 Hz at 32 °C to evaluate the linear viscoelastic properties of the cured adhesives.

### 2.2.3 Morphology of glycerol-silicone adhesives

A Leica TCS SP5 X confocal microscope was used to investigate the morphology of cured composites. The composites were labelled with differently colored dyes in the manufacturing process: sulforhodamine B (0.1 wt.% relative to glycerol) for the glycerol phase, and perylene (10 µL of a perylene solution in
isopropanol 2.53 mg/mL) for the silicone phase. To determine the average size distribution of the spherical glycerol droplets in the formulations, droplet diameters were measured by counting the droplets directly from microscopy pictures using ImageJ software.

2.2.4 NMR studies

For NMR studies, HPβCD:Oct samples ($r = 2$) were dissolved in D$_2$O in a concentration of 20 mg/mL. All NMR spectra were acquired using a Bruker 300 MHz spectrometer at 293 K. For 1D $^1$H NMR, 16 to 128 scans were collected. 2D Rotating frame Overhauser Effect SpectroscopY (ROESY) spectra were collected using a mixing time of 200 ms for detection of intermolecular nuclear overhauser effects (NOEs). 16 scans were collected for each spectrum. Data were analyzed using TopSpin version 3.5 pl 7 from Bruker. The $^1$H NMR prediction software package in ChemOffice 2016 was used as an aid in assigning peaks.

2.2.5 Release profiles of glycerol-silicone adhesives

Oct release profiles from glycerol-silicone adhesives were obtained by immersing specimens containing various amounts of glycerol in deionized water. Measurements were performed at room temperature. Oct release was monitored by measuring the changes in Oct concentration of the aqueous solution. A UV-vis spectrophotometer POLARstar Omega microplate reader (BMG LabTech) was used for the tests, and measurements were translated into concentrations using a calibration curve for aqueous HPβCD:Oct solutions. Oct quantification was performed at 280 nm (CDs did not show any absorbance peak in the UV-vis spectrum).

2.2.6 Antimicrobial properties of adhesives

Antimicrobial tests on glycerol-silicone adhesives containing HPβCD:Oct mixtures ($r = 2$) were performed using a modified version of the ISO22196 method. *P. Aeruginosa* (ATCC 27853) and *E. Coli* (ATCC 53498) bacteria strains were chosen for the tests and grown in a 0.9 wt.% NaCl solution. 200 µL of bacteria-containing solution was then placed on the bottom of a cell culture plate, and discs of cured adhesive (diameter 0.34 mm, thickness 0.3 mm) were put in contact with the liquid. Samples without HPβCD:Oct and a commercial product containing silver, Mepitel Ag, were used as controls. Tests were run in triplicate for each sample. Samples in direct contact with bacteria solutions were allowed to incubate for 24 h in a humid environment. After incubation, the samples were washed with 1.8 mL of 2 wt.% lecithin solution to neutralize Oct activity (according to the US Pharmacopeia). Samples of the liquid were then plated onto agar, incubated for 18-26 h at 35 °C, and CFU (colony forming units) were counted manually. Microbial concentrations were determined using a Biochrom WPA CO8000 Cell Density Meter. The reduction of
microorganisms relative to initial concentrations was calculated and expressed in terms of ‘Log$_{10}$ CFU’. A description of the expressions to determine ‘Log$_{10}$ CFU’ is provided in the Supplementary Information.

3. Results and discussion

3.1 Investigation of the best molar ratio CDs:Oct through the evaluation of the curing profiles of glycerol-silicone adhesives

Because Oct contains two amine groups (Figure 1C), it is an inhibitor of the Pt catalyst involved in hydrosilylation curing. Thus, if Oct is added directly to the silicone adhesive premix, curing does not proceed beyond gelation; in other words, crosslinking does not occur. A novel synthesis strategy is therefore needed that does not include toxic components, such as the less sensitive tin catalyst. One possibility is to add Oct in a different phase than the Pt catalyst, which is possible with glycerol-silicone adhesives. However, even if Oct is predominantly in the glycerol phase, its presence at the glycerol-silicone interface inhibits the curing of the silicone phase. For this reason, we used CDs to screen the Oct from the Pt. Two different CDs were investigated here: βCD and HPβCD (Figure 1A). The influence of CDs:Oct ratio on gelation time, which measures the transition from liquid to solid, and elastic modulus after full cross-linking—were evaluated to find the optimal concentration of CDs in the system.

Glycerol-silicone adhesives’ gelation time and elastic modulus after curing are reported in Figure 2 (A-B) as a function of CDs:Oct ratio. The samples are compared to the corresponding complex-free compositions, i.e., with no CDs or Oct. The curing profiles of pure glycerol-silicone adhesives are shown in Figure S1 (Supplementary Information). As expected, the pure glycerol-silicone adhesives have different gelation times due to their different volume fractions of elastically active material. The pure silicone adhesive reaches gelation in 100 s, and gelation time is shortened when the glycerol content is increased. This is due to the fact glycerol droplets in the soft silicone adhesive premixes contribute to elasticity in the liquid state due to their interfacial energies, introducing a so-called solid stiffening effect.$^{4,29}$ In principle, the larger the number and smaller the size of the glycerol droplets, the greater the elastic contribution. The cross-over over $G'$ and $G''$, which is commonly used as measures of gelation time$^{9,30}$, is reached before the true gelation of the silicone phase due to the elastic contribution from the interfaces. The curing
profile of G50 is made from a different batch of silicone adhesive, and the gelation time is therefore not consistent with the remaining data. An even lower gelation time would be expected if these samples were from the same adhesive batch.

Gelation times were found to decrease and elastic moduli to increase with increasing CDs:Oct ratio (Figure 2, A-B). When \( r = 2 \) and 4, gelation times and elastic moduli are comparable to or higher than those of the corresponding complex-free compositions. In particular, the elastic modulus of G20 increases from approximately 4000 Pa to over 5000 Pa when \( r = 2 \) and 4 (Figure 2B). Oct amounts are always 1 wt.% of overall mass. The mass of silicone decreases from G20 to G50 due to dilution with glycerol, but the Pt:silicone ratio remains constant for all compositions. However, this means that the Pt:Oct ratio is lower in compositions with higher glycerol content, which also have increased surface areas (the effect of glycerol surface area on mechanical properties is discussed in detail in section 3.3). HPβCD allows for the formation of CDs:Oct complexes with \( r \) up to 4, while βCD only allows complex formation for \( r \) up to 1 due to its lower solubility in glycerol compared to HPβCD. As Figure 2B shows, higher CDs:Oct ratios allow adhesives to reach elastic moduli comparable to those of the corresponding reference samples. Importantly, the elastic moduli of adhesives containing CDs:Oct ratios of 2 and 4 are comparable. This indicates that Pt inhibition is sufficiently suppressed at the lower ratio to ensure efficient cross-linking. Further increasing CDs content only changes the apparent gelation time due to the higher initial \( G' \) of the premixes. To better understand the interaction between CDs and Oct at one of the favorable ratios—which, as mentioned previously, can only be achieved with HPβCD—a model NMR study of the system HPβCD:Oct with \( r = 2 \) was conducted using ROESY spectroscopy in the following section.
Investigation of the optimum CDs:Oct ratio through evaluation of gelation times and elastic moduli after full cross-linking. Measurements were conducted in the linear viscoelastic regime at 2% strain. All data was obtained from the curing profiles at 80 °C at a frequency of 2 Hz. A) Gelation times of glycerol-silicone adhesives as a function of CDs:Oct molar ratio and as a function of the glycerol amount. Horizontal lines correspond to gelation times of the complex-free, i.e. with no CDs or Oct, reference compositions. B) Elastic moduli of glycerol-silicone adhesives as a function of CDs:Oct molar ratio and as a function of glycerol amount. Horizontal lines correspond to the elastic moduli of the reference compositions.

### 3.2 2D ROESY of HPβCD:Oct complexes

Guest-host complexes between CDs and various guest molecules are examined using spectroscopic techniques such as NMR, which enable determination of the complexation constant and complex stoichiometry. However, the characterization of HPβCD:Oct complexes is potentially more complicated than that of other CDs:drug systems for several reasons: in order to suppress chemical shift effects from surfactant micellization, complex formation should ideally be analyzed below the critical micelle concentration (CMC), which is reported to be 3.79 mM for Oct. Due to NMR’s relatively low sensitivity, however, getting reliable measurements at such low concentrations requires a specific instrumental setup. In addition, there are reports that structurally similar gemini surfactants may form complexes with either one or two CDs, which would invalidate the use of the common Job’s plot for determining complex stoichiometry. More importantly, NMR studies of HPβCD are complicated by the...
fact that this molecule consists of a number of closely related isomers, which gives the resulting spectrum relatively broad features rather than well-defined sharp peaks.\textsuperscript{35}

Despite these complications, NMR was used to provide further details on the complexation between Oct and HP\(\beta\)CD \((r = 2)\) in deuterated water \((D_2O)\). Initially, 1D \(^1\text{H}\) NMR and 2D COSY spectra were acquired separately for Oct and HP\(\beta\)CD (Figure 3, A-B). As reported, the \(^1\text{H}\) NMR spectrum of HP\(\beta\)CD exhibits several broad features between 3 and 4.5 ppm that do not allow for the exact assignment of individual protons.\textsuperscript{35}

On the other hand, the 1D \(^1\text{H}\) NMR 2D COSY spectra of HP\(\beta\)CD:Oct in D\(_2\)O allow full assignment of several protons for this compound (Figure 3B). In particular, both the aromatic protons and methylene protons \(\alpha, \beta\) and \(\omega\) to the nitrogen atoms can be assigned based on the combination of COSY, comparison to known compounds, and chemical prediction software. The assigned structure is given in Figure 3A.

The complexation between Oct and HP\(\beta\)CD was investigated using ROESY spectroscopy, a technique which exploits the nuclear overhauser effect (NOE) to detect through-space interactions between protons.\textsuperscript{36} The signal intensity scales with distance to the minus sixth \((r^{-6})\), and is therefore highly sensitive to the average distance between protons. In practice, however, distances above 4 Å do not give rise to any signal.\textsuperscript{31} Figure 3 (C-D) shows the ROESY spectrum of a HP\(\beta\)CD:Oct mixture with \(r = 2\) in blue. This is superimposed on ROESY spectra of Oct (red) and HP\(\beta\)CD (black) in order to visualize additional signals in the mixture, indicating little distance between the two molecules.

Due to the broad signals that HP\(\beta\)CD generates, it is impossible to determine exactly which protons in the CD interact with Oct—i.e., whether the interaction is associated with cavity protons or external protons—limiting the possibility of exactly elucidating the complex structure. However, several conclusions can be drawn from the highlighted interaction regions in Figure 3 (C-D). In particular, protons \(a\) (region III), \(g\) (region IV) and \(i\) (region II) show greater interaction with HP\(\beta\)CD than protons \(l\) (region V, compare with region IV) and \(j\) (region I, compare with region II). Protons \(a\) and \(g\) are assigned to the terminal chains and protons \(i\) are ortho to the terminal chain, whereas protons \(l\) are assigned to the central chain and protons \(j\) are ortho to the polar pyridinium group. These results indicate that the terminal chains are particularly associated with the hydrophobic HP\(\beta\)CD cavity and that the aromatic ring constitutes the interface with the exterior, with the charged group being stabilized by the more polar environment. These findings are consistent with reports on complexes between structurally related gemini bis-(dodecyl dimethylammonium)diethyl ether dibromide surfactants and \(\beta\)-CDs.\textsuperscript{33} Due to the lack of fine structure in the spectral features of HP\(\beta\)CD, the ROESY spectrum cannot determine whether one or two HP\(\beta\)CDs complex to the Oct. However, previous work on related gemini complexes has indicated that complexes
with both one and two CDs are possible, corresponding to one or both terminal chains embedded in the hydrophobic part of the CD.\textsuperscript{33} Complexes containing four β-CDs were also reported for a naphthalene-containing cationic gemini surfactant.\textsuperscript{37}

While elucidating the exact complex structure is beyond the scope of this work, the ROESY spectra do clearly indicate that Oct’s aniline groups interact strongly with the HPβCD. This interaction should suppress competitive complexation with the Pt catalyst, thereby suppressing inhibition of the polymerization process. Importantly, however, this argument is only valid if the HPβCD:Oct mixture has a similar structure in glycerol. Unfortunately, acquisition of high-quality ROESY spectra in glycerol was not feasible due to the high viscosity of this solvent combined with a significant overlap between residual solvent signal and HPβCD. However, based on the observation that the solubility of Oct in glycerol is significantly increased in the presence of HPβCD, as well as the results from the curing experiments described in Figure 2 (A-B), it can be assumed that similar complexation occurs in this solvent.

Figure 3. Characterisation of HPβCD:Oct 2:1 mixture by \textsuperscript{1}H NMR. A) Assigned structure of Oct. B) \textsuperscript{1}H NMR spectrum of HPβCD:Oct (r = 2) mixture in D\textsubscript{2}O. C) Enlarged region of ROESY spectrum emphasizing through-space (NOE) interaction between aromatic Oct signals and cyclodextrin. D) Enlarged region of ROESY spectrum emphasizing through-space.
3.3 Evaluation of the linear viscoelastic properties of glycerol-silicone adhesives containing CDs:Oct mixtures

To investigate how the incorporation of CDs:Oct into glycerol-silicone adhesives affects their mechanical behavior, shear rheology in the linear regime was performed. The full spectra of storage moduli (\(G'\)) and viscous moduli (\(G''\)) are shown in Figures S2 and S3 in the Supplementary Information. Dissipation factors (\(\tan \delta = G''/G'\)) are shown in Figure 4 (A-D) as a function of both CDs:Oct ratio and glycerol content (as a reference).

![Graphs showing \(\tan \delta\) for different samples](image)

**Figure 4.** Linear viscoelastic properties of adhesives. Measurements were conducted with controlled strain at 2\% and frequency sweeps from 100 Hz to 0.1 Hz at T = 32 °C. A) \(\tan \delta\) of glycerol-silicone adhesives containing 20, 40 and 50 phr, respectively, compared to a pristine silicone adhesive sample. B-D) \(\tan \delta\) of G20, G40, and G50 adhesives, respectively, containing CDs:Oct mixture with \(r\) ranging from 0.25 to 4.
Counterintuitively, Figure 4A shows that tan δ decreases across the entire frequency range when liquid content increases. In other words, the composites become more solid with increased liquid content. Such behavior has previously been observed for glycerol-silicone adhesives with increasing glycerol content, and can be explained by the fact that the cross-linked emulsions have two distinct elastic components: the elasticity arising from the silicone network itself, and the interfacial energy between the two phases. Style et al. and the extended Eshelby theory previously described this so-called solid-stiffening effect caused by the glycerol droplets in soft silicone elastomers. They demonstrated that surface tension helps to keep liquid inclusions spherical, opposing any applied force that would make them elliptical. Furthermore, the mechanical response of an isolated liquid inclusion depends on its size. In particular, when comparing two soft elastomers with the same interfacial area, the one with smaller droplets is the stiffer of the two. According to the extended Eshelby theory, the length \( l \) and the width \( w \) of a stretched droplet embedded in an elastic solid can be calculated via the equations given below:

\[
l = 2R \left[ 1 + \frac{5(2\epsilon_1 - \epsilon_2)}{6 + 15\frac{\gamma}{ER}} \right]
\]

and

\[
w = 2R \left[ 1 + \frac{5(2\epsilon_2 - \epsilon_1)}{6 + 15\frac{\gamma}{ER}} \right]
\]

\( R \) is the radius of the droplet, \( \epsilon_1 \) and \( \epsilon_2 \) are the applied far-field plane-stress boundary conditions for which \( \epsilon = \epsilon^\infty, \epsilon_1 = \left(\frac{\epsilon^\infty + \nu \epsilon^\infty y}{1 - \nu^2}\right) \) and \( \epsilon_2 = \left(\frac{\epsilon^\infty + \nu \epsilon^\infty x}{1 - \nu^2}\right) \), \( x \) and \( y \) are the strain directions, and \( \nu \) is the Poisson’s ratio; \( \gamma \) is the surface tension of the droplet and \( E \) is the Young’s modulus of the solid. If \( \gamma/ER \gg 1 \), the effect of the surface tension which keeps the droplets spherical is predominant. The effect of CDs incorporated into glycerol-silicone adhesives is investigated further in Figure 4 (B-D). A higher elastic response—i.e. a lower tan δ—is observed for adhesives containing HPβCD:Oct mixtures with \( r > 1 \), indicating that a change in the interfacial energies has occurred. To investigate whether the presence of HPβCD affects the size of the glycerol droplets, adhesives’ morphology was analyzed. Confocal microscopy images of cross-sections of cured adhesives containing a HPβCD:Oct mixture with \( r = 2 \), the relative internal glycerol surface area per adhesive volume, and tan δ (measured at 1 Hz) are shown in Figure 5 (A-C). Confocal image analysis confirms that the average droplet diameter decreases for samples containing HPβCD:Oct compared to their pure counterparts, resulting in a greater glycerol surface area per volume (Figure 5B). This is not surprising, as CDs are known to cause a stabilizing effect in
In addition, adhesives containing HPβCD possess lower tan δ compared to pure compositions (Figure 5C), most likely due to their increased interfacial area.

**Figure 5.** A) Confocal microscopy pictures of cured glycerol-silicone adhesives without (top) and with (bottom) HPβCD:Oct mixtures. All compositions with HPβCD:Oct contain 1 wt.% of Oct and r of 2. Scale bars correspond to 100 µm. B) Glycerol surface area per adhesive volume with and without HPβCD:Oct (r = 2) as a function of glycerol loading. C) Tan δ at 1 Hz of adhesives with and without HPβCD:Oct (r = 2) as a function of glycerol loading. Measurements were conducted with controlled strain of 2% at 32 °C.

To better understand how interfacial energies affect elasticity, we further analyzed the adhesives’ dynamics. The characteristic frequency, \( \omega_{\text{max}} \), at which \( \frac{d (\tan \delta)}{d\omega} = 0 \), is shown for pure glycerol-silicone adhesives and for drug-containing ones in Figures 6A and 6B, respectively. For pure glycerol-silicone adhesives, \( \omega_{\text{max}} \) increases in correlation to glycerol loading. In other words, the relaxation dynamics within the adhesive speed up when glycerol loading increases, while overall elasticity is also increased. Such behavior contradicts classical rubber elasticity theories in which dynamics slow down with increasing elasticity, emphasizing the importance of interfacial contributions to elasticity for these very soft materials. Indeed, these findings indicate that interfacial energies contribute significantly to the higher mobility observed at the glycerol-silicone interface compared to in the adhesive bulk. The characteristic frequency is not affected in the same manner for adhesives containing CDs:Oct mixtures, and remains constant for G40 and G50 regardless of CDs content (Figure 6B). On the other hand, a drop in characteristic frequency is observed for G20 compositions with high CDs content, indicating that the
CDs interact with the glycerol-silicone interface, either by changing the interfacial energy or by physically hindering free motion of the polymers at the interface. To better understand the influence of interfacial energies on adhesive elasticity, as well as how these energies change when CDs are introduced, the Maxwell relaxation time, $\tau_{\text{max}}$, can be used. The Maxwell model defines the characteristic time by defining \( \tan \delta_{\text{max}} \) as:

$$\tan \delta_{\text{max}} = \frac{1}{\omega_{\text{max}} \tau_{\text{max}}} \tag{4}$$

Where $\tan \delta_{\text{max}}$ and $\omega_{\text{max}}$ are determined as described earlier, and $\tau_{\text{max}}$ is determined and plotted against surface area per volume in Figure 6 (C-D). While $\tau_{\text{max}}$ scales linearly with surface area per volume for pure glycerol-silicone adhesives (Figure 6C), the same linearity is not achieved for compositions containing CDs:Oct mixtures (Figure 6D), further suggesting that CDs and/or drugs interact with the interface. Since curing of the silicone adhesive was made possible by the efficient screening described previously, it must be the CDs that interact with the interface to reduce interfacial energies, also leading to the smaller elastic contribution observed for the samples, particularly the adhesives with HPβCD (Figure 2B).
Figure 6. A-B) Characteristic frequency, $\omega_{\text{max}}$, as a function of glycerol loading and CDs:Oct ratio, respectively. C-D) Characteristic relaxation times, $\tau_{\text{max}}$, determined from the Maxwell model as function of the glycerol surface area per volume adhesive without (C) and with HPβCD:Oct ($r = 2$) (D), respectively.

3.4 Release profiles of Oct from glycerol-silicone adhesives and antimicrobial activity

As reported previously, glycerol-silicone composites can absorb significant amounts of water and thereby increase volume while simultaneously releasing small quantities of glycerol upon contact with an aqueous phase.\textsuperscript{4,23,45} It is therefore expected that substances incorporated into glycerol domains will be released from the matrix, as glycerol domains act as reservoirs for these substances. Release profiles of Oct complexed with HPβCD at a ratio of $r = 2$ from glycerol-silicone adhesives with different glycerol contents are shown in Figure 7A. The corresponding release rates are plotted against glycerol content in Figure 7B. The results indicate that Oct is released faster from adhesives with higher glycerol content, in agreement with previously published findings for elastomers. Adhesives were subsequently tested for antimicrobial
activity against *P. Aeruginosa* and *E. Coli* bacteria strains, both of which are common wound pathogens. Bacterial colony growth on agar plates is shown in Figure 7 (C-D). While large bacterial colonies were present for both the pristine G50 sample and the commercial sample containing silver, Mepitel Ag, no colonies were visible for G50 samples containing HPβCD:Oct with \( r = 2 \). For the modified G50 samples, the reduction of microorganisms relative to their initial amount, expressed as ‘Log\(_{10}\) CFU’, was 6 for *P. Aeruginosa* and 5 for *E. Coli*, indicating fully antimicrobial activity against both bacteria strains. No antimicrobial activity was observed for G20 samples loaded with Oct (data not shown), suggesting that the G20 samples did not achieve the minimum release rate required to efficiently kill the given bacteria.
Figure 7. A) Oct release profiles for G20, G40 and G50 glycerol-silicone adhesives with HPβCD:Oct ratio equal to 2. B) Release rate dependence on glycerol content. C-D) Bacteriological results of ISO2219 tests
and ‘Log_{10}CFU’ of the commercial samples and G50_Oct 1 wt.% (HPβCD:Oct with $r = 2$), respectively. The adhesive samples were in direct contact with 200 µL of bacteria solutions containing *P. Aeruginosa* and *E. Coli*, respectively, for 24 h. Visible colonies appeared on both G50 samples without Oct and the commercial samples exposed to bacteria for 24 h after the liquid samples were plated onto agar. No colonies were visible after bacteria exposure of G50_Oct 1 wt.% (HPβCD:Oct with $r = 2$).

4. Conclusion

We developed a novel antimicrobial glycerol-silicone adhesive capable of releasing Oct via CDs. Oct incorporation was achieved via CDs through formation of an inclusion complex with the drug. Rheological characterization of glycerol-silicone adhesives with varying CDs:Oct ratios showed that HPβCD:Oct complexes with a ratio > 1 allowed incorporation of 1 wt.% of Oct without compromising adhesives’ mechanical properties. The interaction between HPβCD and Oct via an inclusion complex was further characterized and confirmed using ROESY spectroscopy. Finally, we demonstrated the possibility of releasing Oct from glycerol-silicone adhesives, and showed that a minimum release rate, obtained in G50 samples, is required to kill bacteria. Fully antimicrobial activity against *P. Aeruginosa* and *E. Coli* was achieved through G50 samples containing HPβCD:Oct in a molar ratio equal to 2.

Due to the favorable properties they display, together with their relatively simple preparation process, glycerol-silicone adhesives with Oct incorporated via CDs should be considered potential candidates for advanced wound care applications, in which it is necessary to both effectively promote wound healing and prevent bacterial infection.

5. Acknowledgements

The authors gratefully acknowledge the financial support of V.C. from The Innovation Fund Denmark. Furthermore, the authors acknowledge Coloplast scientists Lotte Stoklund Jensen, for assistance with antimicrobial tests, and Rasmus Irming Jølck, for valuable scientific discussions. Finally, the authors acknowledge the Center for Advanced Bioimaging (CAB) at University of Copenhagen (DK) for the image data collection.
6. References


Supporting Information

for

**Novel Antimicrobial Glycerol-Silicone Adhesives Releasing Octenidine**

**Incorporated via Cyclodextrins**

V. Chiaula\(^a\), J. Madsen\(^a\), P. Mazurek\(^a\), A. C. Nielsen\(^b\), A. L. Skov\(^a*\)

\(^a\) Danish Polymer Centre, Department of Chemical and Biochemical Engineering, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark.

\(^b\) GRD Technology – Adhesives, Coloplast A/S, DK-3050 Humlebæk, Denmark.

Keywords: hydrosilylation, platinum catalyst, cyclodextrins, glycerol, silicone, adhesives, release

\(^*\) Corresponding author: al@kt.dtu.dk

1. **Log reductions in antimicrobial testing**

When calculating the number of bacteria it is common to use a logarithmic scale. The ‘Log Reduction’, usually reported as ‘Log\(_{10}\) CFU’ in antimicrobial testing, is defined as:

\[
Log_{10} CFU = \log_{10} \frac{A}{B}
\]  

(1)

where A corresponds to the number of viable microorganism before testing, and B is the number of viable microorganisms after testing.

2. **List of investigated adhesive samples**

A full description of all investigated samples can be found in Table 1.

**Table 1.** List of investigated samples with the corresponding sample names.
<table>
<thead>
<tr>
<th>Sample name</th>
<th>Glycerol phr</th>
<th>Octenidine amount</th>
<th>Type of cyclodextrin</th>
<th>Molar ratio CD:Oct</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0</td>
<td>0</td>
<td></td>
<td>βCD</td>
<td>1:4</td>
</tr>
<tr>
<td>G20</td>
<td>20</td>
<td></td>
<td>βCD</td>
<td>1:2</td>
</tr>
<tr>
<td>G20</td>
<td>40</td>
<td></td>
<td>βCD</td>
<td>1:1</td>
</tr>
<tr>
<td>G50</td>
<td>50</td>
<td></td>
<td>βCD</td>
<td>1:1</td>
</tr>
<tr>
<td>G20_Oct 1 wt.% (βCD:Oct_0.25)</td>
<td>20</td>
<td>1 wt. %</td>
<td>βCD</td>
<td>1:4</td>
</tr>
<tr>
<td>G20_Oct 1 wt.% (βCD:Oct_0.5)</td>
<td>20</td>
<td>1 wt. %</td>
<td>βCD</td>
<td>1:2</td>
</tr>
<tr>
<td>G20_Oct 1 wt.% (βCD:Oct_1)</td>
<td>20</td>
<td>1 wt. %</td>
<td>βCD</td>
<td>1:1</td>
</tr>
<tr>
<td>G20_Oct 1 wt.% (HPβCD:Oct_0.25)</td>
<td>20</td>
<td>1 wt. %</td>
<td>HPβCD</td>
<td>1:4</td>
</tr>
<tr>
<td>G20_Oct 1 wt.% (HPβCD:Oct_0.5)</td>
<td>20</td>
<td>1 wt. %</td>
<td>HPβCD</td>
<td>1:2</td>
</tr>
<tr>
<td>G20_Oct 1 wt.% (HPβCD:Oct_1)</td>
<td>20</td>
<td>1 wt. %</td>
<td>HPβCD</td>
<td>1:1</td>
</tr>
<tr>
<td>G20_Oct 1 wt.% (HPβCD:Oct_2)</td>
<td>20</td>
<td>1 wt. %</td>
<td>HPβCD</td>
<td>2:1</td>
</tr>
<tr>
<td>G20_Oct 1 wt.% (HPβCD:Oct_4)</td>
<td>20</td>
<td>1 wt. %</td>
<td>HPβCD</td>
<td>4:1</td>
</tr>
<tr>
<td>G40_Oct 1 wt.% (βCD:Oct_0.25)</td>
<td>40</td>
<td>1 wt. %</td>
<td>βCD</td>
<td>1:4</td>
</tr>
<tr>
<td>G40_Oct 1 wt.% (βCD:Oct_0.5)</td>
<td>40</td>
<td>1 wt. %</td>
<td>βCD</td>
<td>1:2</td>
</tr>
<tr>
<td>G40_Oct 1 wt.% (βCD:Oct_1)</td>
<td>40</td>
<td>1 wt. %</td>
<td>βCD</td>
<td>1:1</td>
</tr>
<tr>
<td>G40_Oct 1 wt.% (HPβCD:Oct_0.25)</td>
<td>40</td>
<td>1 wt. %</td>
<td>HPβCD</td>
<td>1:4</td>
</tr>
<tr>
<td>G40_Oct 1 wt.% (HPβCD:Oct_0.5)</td>
<td>40</td>
<td>1 wt. %</td>
<td>HPβCD</td>
<td>1:2</td>
</tr>
<tr>
<td>G40_Oct 1 wt.% (HPβCD:Oct_1)</td>
<td>40</td>
<td>1 wt. %</td>
<td>HPβCD</td>
<td>1:1</td>
</tr>
<tr>
<td>G40_Oct 1 wt.% (HPβCD:Oct_2)</td>
<td>40</td>
<td>1 wt. %</td>
<td>HPβCD</td>
<td>2:1</td>
</tr>
<tr>
<td>G40_Oct 1 wt.% (HPβCD:Oct_4)</td>
<td>40</td>
<td>1 wt. %</td>
<td>HPβCD</td>
<td>4:1</td>
</tr>
<tr>
<td>G50_Oct 1 wt.% (βCD:Oct_0.25)</td>
<td>50</td>
<td>1 wt. %</td>
<td>βCD</td>
<td>1:4</td>
</tr>
<tr>
<td>G50_Oct 1 wt.% (βCD:Oct_0.5)</td>
<td>50</td>
<td>1 wt. %</td>
<td>βCD</td>
<td>1:2</td>
</tr>
<tr>
<td>G50_Oct 1 wt.% (βCD:Oct_1)</td>
<td>50</td>
<td>1 wt. %</td>
<td>βCD</td>
<td>1:1</td>
</tr>
<tr>
<td>G50_Oct 1 wt.% (HPβCD:Oct_0.25)</td>
<td>50</td>
<td>1 wt. %</td>
<td>HPβCD</td>
<td>1:4</td>
</tr>
<tr>
<td>G50_Oct 1 wt.% (HPβCD:Oct_0.5)</td>
<td>50</td>
<td>1 wt. %</td>
<td>HPβCD</td>
<td>1:2</td>
</tr>
<tr>
<td>G50_Oct 1 wt.% (HPβCD:Oct_1)</td>
<td>50</td>
<td>1 wt. %</td>
<td>HPβCD</td>
<td>1:1</td>
</tr>
<tr>
<td>G50_Oct 1 wt.% (HPβCD:Oct_2)</td>
<td>50</td>
<td>1 wt. %</td>
<td>HPβCD</td>
<td>2:1</td>
</tr>
<tr>
<td>G50_Oct 1 wt.% (HPβCD:Oct_4)</td>
<td>50</td>
<td>1 wt. %</td>
<td>HPβCD</td>
<td>4:1</td>
</tr>
</tbody>
</table>
3. Curing profiles of pure glycerol-silicone adhesives

Curing profiles of pure glycerol-silicone adhesives are shown in Figure S1. For all the tested adhesive, the cross-over point is reached between 60 and 140 s.

![Curing profiles of glycerol-silicone adhesives](image)

*Figure S1.* Curing profiles of glycerol-silicone adhesives. Measurements were conducted in the linear viscoelastic regime and 2% strain. All data is obtained from the curing profiles at 80 °C at a frequency of 2 Hz.

4. Evaluation of the linear viscoelastic properties of glycerol-silicone adhesives containing CD₅:Oct mixtures

To investigate the influence of CD₅:Oct mixtures on the mechanical properties of glycerol-silicone adhesives, storage moduli (G’) and viscous moduli (G”’) as a function of frequency are reported in Figure S2 and S3. Data shows that the adhesives have a relatively lower elastic response and a larger viscous response for adhesive with CD₅:Oct of r < 1, independently of the type of CD. For CD:Oct mixtures with r > 1, a slight increase of G’ is observed.
Figure S2. Storage moduli of adhesives containing βCD:Oct and HPβCD:Oct and mixtures with r ranging...
from 0.25 to 4 compared to drug-free compositions. Measurements were conducted with controlled strain at 2% and frequency sweeps from 100 Hz to 0.1 Hz at T = 32 °C.

**Figure S3.** Viscous moduli of adhesives containing βCD:Oct and HPβCD:Oct and mixtures with r ranging from 0.25 to 4 compared to drug-free compositions. Measurements were conducted with controlled strain at 2% and frequency sweeps from 100 Hz to 0.1 Hz at T = 32 °C.

To better visualize the influence of r on the linear viscoelastic properties, G’ and tan δ recorded at 1 Hz are plotted versus r (Figure S4). 1 Hz frequency was chosen because it is a sufficiently fast frequency to allow sampling. In general, an increase of G’ and a decrease of tan δ are observed for CD’s:Oct mixtures with r > 1. The data support the hypothesis that the presence of CDs in higher molar amounts compared to Oct suppresses the interference of Oct with the Pt catalyst, thereby increasing the catalyst efficiency in the hydrosilylation curing reaction.
Figure S4. Elastic moduli and tan δ at 1 Hz of glycerol-silicone adhesives as a function of the molar ratio of CDs:Oct mixtures with \( r \) ranging from 0.25 to 4, at \( T = 32 \, ^\circ C \) and strain 2%.

To complete our analysis on the influence of the interfacial energies on the elasticity of adhesives, and how these energies change when CDs are introduced, \( \omega_{\text{max}} \), which is the frequency where tan δ has its maximum, is plotted against the glycerol surface area per volume of adhesive in Figure S5.

Figure S5. Angular frequency \( \omega_{\text{max}} \), i.e. where tan δ has its maximum, as a function of the glycerol surface area per volume of adhesive.